

**A COMPARISON OF OCULAR AND
CERVICAL VESTIBULAR EVOKED
MYOGENIC POTENTIALS**
IN THE EVALUATION OF DIFFERENT STAGES OF
CLINICALLY CERTAIN MÉNIÈRE'S DISEASE

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Abstract

Cervical vestibular evoked myogenic potential (cVEMP) testing is widely used in the assessment of vestibular disorders in clinical practice (Welgampola & Colebatch, 2003). Ocular vestibular evoked myogenic potentials (oVEMPs) are similar to the cervical VEMPs in that the vestibular system is also stimulated by a loud sound. The difference is that the response is measured on the inferior oblique muscle of the eye as opposed to the sternocleidomastoid muscle (SCM) of the neck (Chihara, Iwasaki, Ushio, & Murofushi, 2007). The current study compares the standard cervical VEMP to the ocular VEMP in both control subjects and participants with “clinically certain” Ménière’s disease. By investigating cervical VEMPs in comparison to ocular VEMPs we aimed to improve the ability to stage and diagnose Ménière’s disease using the ocular VEMP.

22 control participants and 19 participants with confirmed unilateral Ménière’s disease took part in the study. The peak latency and amplitudes of the ocular and cervical VEMP tests were recorded and analysed. In addition, the background electromyographic (EMG) activity of both the inferior oblique and sternocleidomastoid muscles was recorded throughout testing. A questionnaire was also distributed to all participants to compare the relative difficulty of the VEMP tests. Statistical analysis using the paired t-test, standard t-test and the one-way ANOVA on ranks test was applied to determine a difference between the control and patient groups for both the ocular and cervical VEMP tests.

Overall, the threshold and IAD ratio measures did not produce any significant results when sound was presented to the affected ear for the cervical and ocular VEMP tests. A significant reduction in amplitude of the VEMPs from the Ménière’s groups was found compared to the control groups for the ocular the cervical VEMPs. Overall, an increase in P2 and N3 latency of the ocular VEMP response in Ménière’s patients was determined. Results from the questionnaire suggest that the ocular VEMP test was more tolerable to the cervical VEMP test in this current study. Furthermore, statistical analyses revealed no significant differences in EMG level between the control and Ménière’s group for both the ocular and cervical VEMP data.

Overall, results suggest that both the cervical and ocular VEMP tests provide information regarding the integrity of the saccule, owing to the abnormal VEMP findings in the participants with Ménière's disease. In addition, this study provides evidence that the ocular VEMP is as useful a tool in diagnosing Ménière's disease as the cervical VEMP.

Table of Contents

Acknowledgments.....	i
Abstract.....	ii
TABLE OF CONTENTS.....	1
1. INTRODUCTION.....	4
1.1. THE LABYRINTH OF THE INNER EAR.....	5
1.2. SACCULO-COLLIC REFLEX PATHWAY.....	8
1.3. STANDARD/CERVICAL VESTIBULAR EVOKED MYOGENIC POTENTIAL TESTING.....	9
1.3.1. <i>Stimulus Characteristics</i>	12
1.3.2. <i>Presentation of Acoustic Stimuli</i>	13
1.3.3. <i>Dependence on EMG</i>	13
1.3.4. <i>Electrode Placement</i>	13
1.3.5. <i>Effect of Age and Gender</i>	14
1.4. MÉNIÈRE’S DISEASE.....	15
1.4.1. <i>Electrocochleography and Ménière’s Disease</i>	21
1.5. MÉNIÈRE’S DISEASE AND CERVICAL VESTIBULAR EVOKED MYOGENIC POTENTIALS.....	23
1.6. VESTIBULO-OCULAR REFLEX PATHWAY.....	25
1.6.1. <i>Ocular Vestibular Evoked Myogenic Potentials</i>	27
1.7. AIMS OF THE PROPOSED STUDY.....	30
2. METHOD.....	32
2.1. PARTICIPANTS.....	32
2.1.1. <i>Electrocochleography (ECochG)</i>	34
2.2. INSTRUMENTATION.....	36
2.2.1. <i>Vestibular Evoked Myogenic Software</i>	36
2.3. CALIBRATION.....	39
2.4. PROCEDURE.....	39
2.4.1. <i>Tympanometry</i>	39
2.4.2. <i>Pure-tone Audiometry</i>	40
2.4.3. <i>Cervical Vestibular Evoked Myogenic Potential Testing</i>	40
2.4.4. <i>Ocular Vestibular Evoked Myogenic Potential Testing</i>	43
2.5. MEASURES.....	45
2.5.1. <i>Threshold</i>	45
2.5.2. <i>Amplitude</i>	45
2.5.3. <i>Latency</i>	46
2.5.4. <i>Interaural Amplitude Difference Ratio</i>	46
2.5.5. <i>Electromyographic Activity</i>	46
2.5.6. <i>Questionnaire</i>	46
2.6. STATISTICAL ANALYSIS OF RESULTS.....	47
3. RESULTS.....	49
3.1. THRESHOLD.....	49
3.2. AMPLITUDE AND PEAK-TO-PEAK AMPLITUDE MEASURES.....	52
3.2.1. <i>Amplitude and Peak-to-peak Amplitude Measures of the Contralateral Ocular VEMP</i>	53
3.2.2. <i>Amplitude and Peak-to-peak Amplitude Measures of the Cervical VEMP</i>	58
3.3. LATENCY MEASURES.....	61
3.3.1. <i>Latency Measures of the Ocular VEMP</i>	61
3.3.2. <i>Latency and Peak-to-peak Latency Measures of the Cervical VEMP</i>	63
3.4. INTERAURAL AMPLITUDE DIFFERENCE RATIO.....	63
3.4.1. <i>Contralateral Ocular VEMP IAD Ratio</i>	63
3.4.2. <i>Ipsilateral Cervical VEMP IAD Ratio</i>	64
3.5. QUESTIONNAIRE.....	64
3.6. EMG.....	65

4. DISCUSSION.....	68
4.1. LATENCY.....	68
4.1.1. <i>Contralateral Ocular VEMP Latency Review</i>	68
4.1.2. <i>Ipsilateral Cervical VEMP Latency Review</i>	69
4.1.3. <i>Summary of Cervical and Ocular VEMP Latency Measures</i>	69
4.2. AMPLITUDE.....	71
4.2.1. <i>Contralateral Ocular VEMP Amplitude Review</i>	71
4.2.2. <i>Ipsilateral Cervical VEMP Amplitude Review</i>	72
4.2.3. <i>Summary of Ocular and Cervical VEMP Amplitude Measures</i>	73
4.3. THRESHOLD.....	74
4.3.1. <i>Ipsilateral Cervical VEMP Threshold Review</i>	74
4.3.2. <i>Contralateral Ocular VEMP Threshold Review</i>	75
4.3.3. <i>Summary of Ocular and Cervical VEMP Thresholds</i>	75
4.4. IAD RATIO.....	76
4.5. POLARITY.....	77
4.6. STAGING.....	79
4.7. CONCLUSION.....	80
4.8. LIMITATIONS.....	82
4.8.1. <i>Participants</i>	82
4.8.2. <i>Technique</i>	84
4.8.3. <i>Equipment</i>	86
4.8.4. <i>Peak Picking</i>	86
4.9. FURTHER DIRECTIONS.....	86
5. REFERENCES.....	87

CHAPTER ONE

INTRODUCTION

1. Introduction

Ocular vestibular evoked myogenic potential (VEMP) testing has recently been developed as a new method for assessing the integrity of the vestibular system (Rosengren, Todd, & Colebatch, 2005; Chihara et al. 2007; Todd, Rosengren, Aw, & Colebatch, 2007). This technique has not yet been used widely clinically, nor has it been applied to primarily assess Ménière's disease. If this technique proves more widely applicable and useful than standard vestibular evoked myogenic potential tests, it is likely to become an integral part of the assessment of vestibular disorders.

Standard vestibular evoked myogenic potential testing is widely used in the assessment of vestibular disorders in clinical practice (Welgampola & Colebatch, 2003). The test requires patients to tense their sternocleidomastoid muscles (SCM) whilst a loud tone is played in their ear. Electrodes on the skin overlying the participant's SCM record a myogenic response as a result of acoustic stimulation of the vestibular system. Ocular vestibular evoked myogenic potentials are similar to the standard VEMP testing in that the vestibular system is also stimulated by a loud sound. The difference is that the response is measured on the inferior oblique muscle of the eye as opposed to the SCM. This study will compare the clinical applicability and diagnostic ability of the standard VEMP to the ocular VEMP in both control subjects and participants with a known vestibular disorder, Ménière's disease.

To determine the ability of the ocular vestibular evoked myogenic potential (oVEMP) test to diagnose Ménière's disease, statistical analysis was applied comparing the amplitude, interaural amplitude difference (IAD) ratio, latency and threshold between the cervical vestibular evoked myogenic potential (cVEMP) and the oVEMP. In order to explain the results of this study and its clinical significance the following discusses the anatomy of the inner ear, in particular the vestibular apparatus and the cochlea. Discussion of the synaptic pathways of the cVEMP response and Ménière's disease follows, including the use of electrocochleography and cervical VEMPs. The oVEMP synaptic pathway and current literature on the oVEMP ensues.

The principle aim of the study was to investigate the ability of the ocular VEMP to diagnose and stage Ménière's disease. It is hypothesised that ocular VEMP testing will be more widely applicable to the general population as the task is less strenuous and is superiorly tolerated

compared to the cervical VEMP (Wang, Jaw, & Young, 2009). In addition, we hypothesise the the ocular VEMP will provide comparable results to the cervical VEMP.

1.1. The Labyrinth of the Inner Ear

The inner ear consists of two key structures; the cochlea and the vestibular apparatus. These structures have separate functions: the cochlea is responsible for the transduction of acoustic stimuli into electrical impulses for neural processing to provide the sense of hearing; while the vestibular apparatus codes rotational and linear head movements into electrical impulses to provide sense of balance. For the coding of acoustic stimuli, sound must first travel through the external auditory meatus and the middle ear before it reaches the oval window. Sound then transverses the oval window and vibrates the basilar membrane within the cochlea. The vibrations are then passed to the cochlear fluids, resulting in a transverse motion of the basilar membrane.

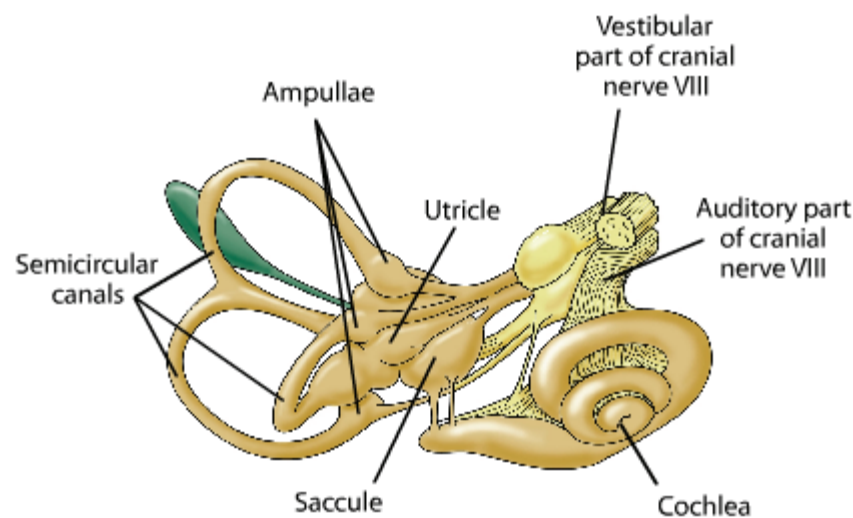
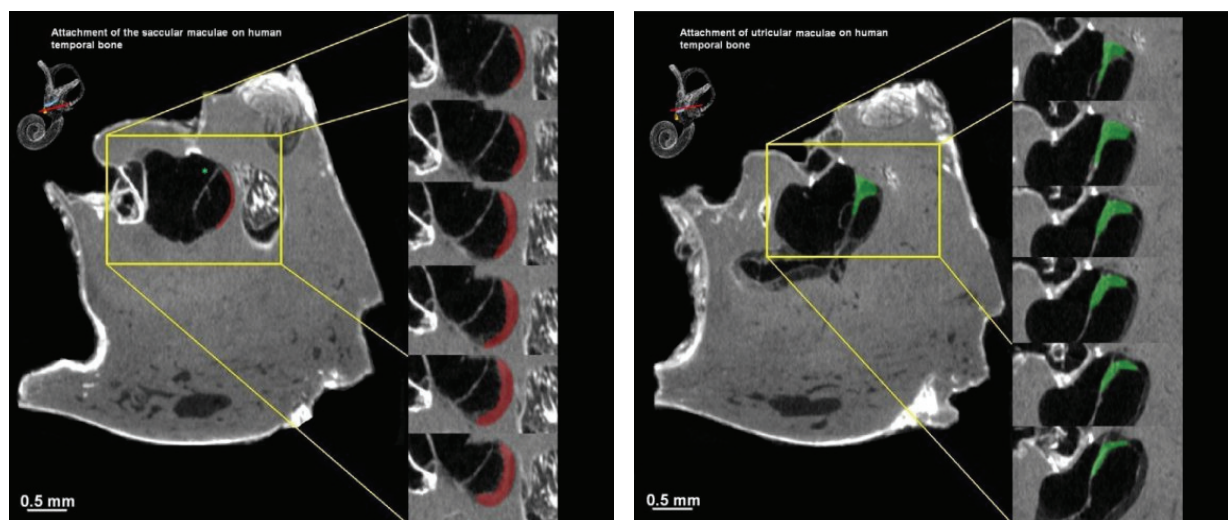


Figure 1.1. Anatomy of the inner ear inclusive of the vestibular system and the cochlea. This representation indicates the position of the three semicircular canals relative to the saccule and utricle. Note, the close proximity of the saccule and cochlea. The auditory and vestibular portions of the cranial nerve, originating from the cochlea and vestibular system respectively, are also evident (Purves, Augustine, Fitzpatrick, Hall, LaMantia, McNamara, & White, 2008).

The vestibular system is situated within a bony labyrinth within each of the temporal bones of the skull. Contained by this bony labyrinth is a membranous labyrinth filled with two fluids, endolymph and perilymph, which have differing ionic compositions. The vestibular labyrinth

consists of five core structures as depicted in Figure 1.1: the three semicircular canals (and their cristae ampullaris) which detect angular rotation, and the utricle and saccule (with their maculae) which detect linear acceleration in the horizontal and vertical planes respectively. In depth investigations of the maculae have revealed a significant difference between the attachments of the utricle and saccule to the temporal bone. The Uzun-Coruhlu, Curthoys, and Jones (2007) investigation suggested that the saccule was firmly attached to the temporal bone whereas only the rostral portion of the utricle was secured (Figures 1.2 and 1.3). The finding that the utricle is essentially free-floating is likely to reflect a difference in sensory transduction compared to the saccule.



Figures 1.2 and 1.3. The attachment of the saccular macula (left) and utricular macula (right) to the temporal bone in the human. These figures indicate that only the rostral portion of the utricular macula is attached to the bone whilst the saccular macula is firmly attached to the bone (Uzun-Coruhlu et al., 2007).

Each of the maculae contains a collection of sensory hair cells that have stereocilia and kinocilia, hair-like projections, on their apex. Resting above the hair cells is the otolithic membrane, which is embedded with calcium carbonate crystals called otoconia, as shown in Figure 1.4 (Furman & Cass, 2003). This otolithic membrane acts as a mass that alters position with a change in head movement, consequently deflecting the stereocilia of the hair cells below (Baloh & Honrubia, 2001). Depolarisation of these sensory hair cells results in excitation of the primary afferent vestibular neurons which in turn excites the vestibular nuclei via the inferior vestibular nerve. The vestibular nuclei then send impulses to stimulate, among others, the ocular motor nuclei, the cerebellum, and motor nuclei in the neck to maintain equilibrium

(Schubert & Shepard, 2008). The VEMP test relies on the fact that the utricle and saccule are not only sensitive to linear acceleration, but also to loud sounds.

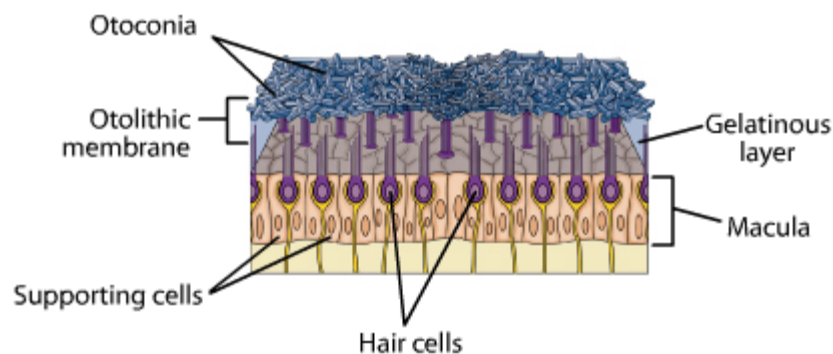


Figure 1.4. Depicts the cellular organisation of the maculae within the utricle and saccule. Resting upon the hair cells lies the otolithic membrane which is made up of a gelatinous layer and calcium carbonate layer (the otoconia). The otoconia can move in response to head movements due to its mass. The movement of this mass moves the tips of the hair cells into either a position of opening or closing which leads to activation or inactivation of the vestibular nerve respectively (Purves et al. 2008).

The saccule of the vestibular system is acoustically responsive due to the anatomical positioning of the saccular sensory cells adjacent to the footplate of the stapes (Mc Cue & Guinan, 1994; Todd, 2001; Murofushi, Curthoys, & Gilchrist, 1996). Acoustic stimulation of the saccule is thought to stimulate inhibitory postsynaptic potentials in the flexor motor neurons of the cervical muscles (Uchino, Sato, Sasaki, Imagawa, Ikegami, Isu, & Graf, 1997). An investigation by McCue and Guinan (1994) sought to determine if a portion of afferent nerve fibres from the saccule respond to acoustic stimuli. To ascertain this, an electrode was placed near the vestibular nerve in a cat. Fibres which increased in their firing rate in response to a loud tone burst were defined as acoustically responsive. 500-1000 Hz tone bursts elicited the greatest firing rate of vestibular fibres. This finding is in accordance with the study by Rauch, Zhou, Kujawa, Wall, Guinan, and Herrmann (2004b), which determined a frequency tuning curve with a peak at 500 Hz for vestibular afferents.

The cochlea is an essential component for the transduction of acoustic stimuli into electrical impulses. The cochlea resides within the temporal bones adjacent to the vestibular systems. An osseous labyrinth lined by a membranous labyrinth connects these two regions of the inner ear. Furthermore, within this membranous labyrinth is a fluid with a high concentration of potassium, namely the endolymph. The cochlea itself is divided into three partitions by

Reissner's membrane and the basilar membrane. Superior to Reissner's membrane is scala vestibuli which consists of a fluid of high sodium content, the perilymph. Scala tympani, directly inferior to the basilar membrane also contains this perilymph fluid. Between these membranes, however is a fluid-filled chamber called the scala media. In contrast to scala tympani and scala vestibuli, scala media contains endolymph (Pickles, 2008).

Situated upon the basilar membrane are multiple rows of outer and inner hair cells. These cells are activated by movement of the basilar membrane, as a result of an acoustic stimulus, relative to the tectorial membrane which lies over the stereocilia (or tips) of these cells. When the basilar membrane vibrates, the tectorial membrane forces the tips of the inner and outer hair cells to move; opening and closing the membrane channels situated in these tips. The result of this shearing action is a change in resistance of the hair cells causing an influx of potassium from the potassium rich scala media. Influx of potassium changes the membrane potential of the inner hair cells which leads to activation of the primary afferent neurons lying underneath. The outer hair cells, however respond differently to this change in membrane potential and alternatively cyclically contract and relax. Contraction of these cells moves the basilar membrane towards the scala vestibuli and increases the overall amplitude of movement of the basilar membrane. This increase in basilar membrane movement results in a further increase in activation of inner hair cells. With an increase in the intensity of the stimulus this transduction method results in greater discharges of neurotransmitter and a resultant increase in the number of primary afferent neurons recruited (Pickles, 2008).

1.2. Sacculo-collic Reflex Pathway

The sacculo-collic reflex pathway is a reflex pathway from the saccule to the muscles of the neck, which is thought to play a role in the maintenance of equilibrium of the head and trunk. Electrical information for this reflex passes from the vestibular apparatus via the inferior vestibular nerve, which originates in the saccule, to the sternocleidomastoid muscle (Basta et al. 2005). Numerous primary vestibular neurons then project onto second order vestibular neurons situated in the ventral and descending portion of the lateral vestibular nucleus as shown in Figure 1.5 (Uchino et al., 1997). Stimulation of the second order vestibular neurons is both inhibitory and excitatory. Therefore, activation of second order vestibular neurons either results in excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (IPSPs)

evoking corresponding contralateral and ipsilateral flexor and extensor neck muscles. Ipsilateral and contralateral flexor muscle motor nuclei of the neck receive inhibitory postsynaptic potentials indirectly from the saccule whilst ipsilateral and contralateral extensor muscle nuclei receive excitatory signals (Ushino et al., 1997). As a result, the agonist muscles of the neck are activated and the antagonist muscles are relaxed and maintenance of head position occurs. Acoustic stimulation of this pathway results in a similar activation of the hair cells in the vestibular system (McCue & Guinan, 1994).

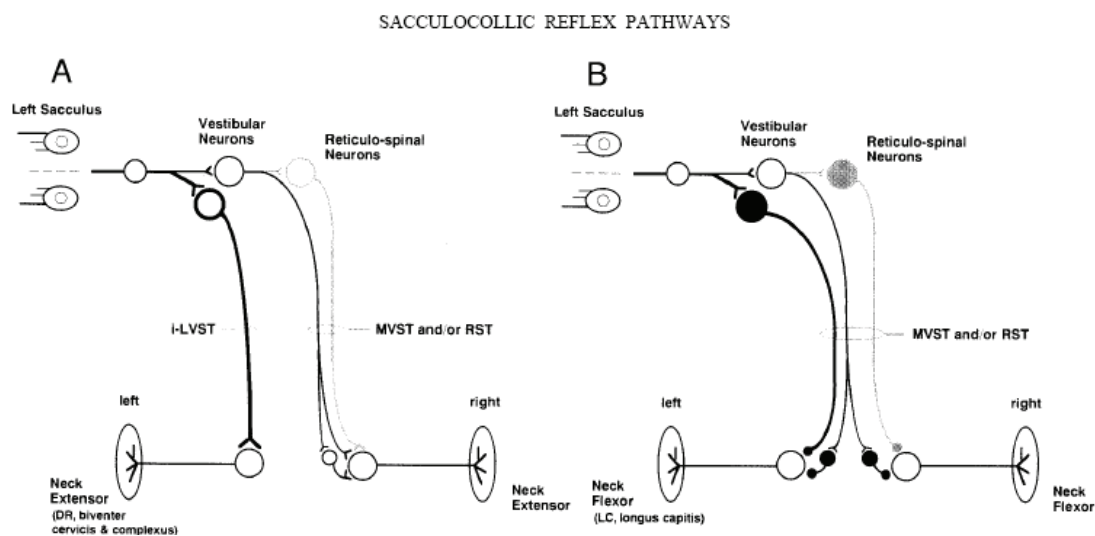


Figure 1.5. Indicates the sacculo-colic reflex pathway. Diagram (A) is the excitatory pathway and (B) is inhibitory. Projections from the saccule via the saccular nerve synapse onto second order vestibular neurons which make direct and indirect connections with the extensor and flexor muscles of the neck (Uchino et al. 1997).

1.3. Standard/Cervical Vestibular Evoked Myogenic Potential Testing

Acoustic stimulation of the vestibular system results in activation of the motor nuclei in the neck and the oculomotor nuclei near the eye, amongst others. Activation of these motor nuclei stimulates the sternocleidomastoid muscle and inferior oblique muscle, respectively. Vestibular evoked myogenic potentials take advantage of this pathway by collecting electrical potentials over these muscles in response to an abrupt acoustic stimulus presented to the labyrinth of the inner ear. The optimal position for recording this evoked potential is directly over the muscle when the muscle is actively contracting. Owing to the fact that the vestibular system is initially stimulated along the sacculo-colic reflex pathway the VEMP can relay information regarding the integrity of the vestibular system, specifically the saccule and vestibular nerve (Rauch et al. 2004b). Pathologies often investigated with standard VEMP include vestibular neuritis, acute

vertigo, superior canal dehiscence, acoustic neuromas, sudden deafness and Ménière's disease (Heide, Freitag, Wollenberg, Iro, Schimrigk, & Dillmann, 1999; Murofushi, Matsuzaki, & Mizuno, 1998; Brantberg, Bergenius, & Tribukait, 1999; Chen & Young, 2006; Rauch, Silveira, Zhou, Kujawa, Wall, Guinan, and Herrmann, 2004a).

Early investigations of the VEMP performed by Geisler, Frishkopf, & Rosenblith (1958) and Bickford, Jacobson, & Cody (1964) recorded an electromyographic potential in the muscles of the neck after intense acoustic stimulation. Subsequent research by Colebatch and Halmagyi (1992) concluded that selective sectioning of the vestibular nerve abolished the VEMP response yet was maintained in patients with a sensorineural hearing loss. Studies following these publications investigated the origin of the pathway and its diagnostic applications. As a result that cervical VEMP test is widely applied as a test of vestibular function (Young, 2006).

Bath, Harris, and Yardley (1998) determined that the presentation of loud clicks resulted in a short latency waveform measured from the SCM (n=32). The size of this waveform was dependent on the degree of activation of the SCM and the level of stimulus intensity. The waveform had a latency of 8 ms and had a clear negative and positive peak. This response is purely a vestibular one as three participants with sensorineural hearing loss also produced the biphasic response. This response is termed the vestibular evoked myogenic response (VEMP) and is dependent on optimally functioning vestibular end organs and afferents. Matsuzaki and Murofushi (2003) administered gentamicin to guinea pigs to destroy the peripheral end organs of the vestibular system and VEMPs and acoustic brainstem responses (ABR) pre and post administration were measured. Post administration, the VEMP response was absent whilst the ABR remained. Similarly, after vestibular nerve section the ABR was preserved whilst the VEMP response was abolished. Furthermore, this is supported by the work of Colebatch, Halmagyi, and Skuse (1994) who also confirmed the absence of the VEMP response in five patients with vestibular nerve section. This response from the vestibular system to the SCM in the neck is a by product of maintaining postural stability via the saccular afferent system to the motor nuclei in this muscle. Since the discovery of vestibular-evoked myogenic potentials in muscles other than the SCM, the SCM response is often called the cervical VEMP (cVEMP), and will be referred to as such in the remainder of this thesis.

Current VEMP testing is applied to determine the integrity of the vestibular apparatus by measuring a large myogenic potential over the sternocleidomastoid muscle (SCM). This involves recording, filtering and amplifying the electromyographic (EMG) signal produced by the muscle. Acoustic stimulation of the vestibular system is the most commonly used technique (Bath et al., 1998; Rauch et al., 2004b; Rauch et al., 2004a) however, bone conduction stimuli, head taps and transmastoid galvanic stimulation can also be applied (Welgampola & Colebatch, 2005). Because the myogenic response relies on muscle tone, in order to measure a response the participant must be actively contracting the SCM, such as by simply raising their head from a supine position. The mean latencies of the initial positive (p1) and negative (n1) waves of the cVEMP, in participants with no known vestibular disorders, are denoted as p13 and n23 respectively due to the polarity and latency of these peaks as seen in Figure 1.6. For example, Wang and Young (2003) demonstrated a p1 latency of 14.43 +/- 1.97 ms and an n1 latency of 21.82 +/- 1.84 ms, and Wang and Young (2004) demonstrated a p1 latency of 14.08 +/- 1.27 ms and an n1 latency of 20.66 +/- 1.52 ms using the ideal stimulation parameters for the VEMP response. Minor variance in the latencies of these peaks do appear in the literature, for example Basta, Todt, and Ernst (2005) determined a mean latency (n=64) of 16.0 +/- 2.0 ms for p1 and 23.5 +/- 2.3 ms for n1 for air conduction stimuli. This Basta et al. (2005) study consisted of 64 participants with a mean age of 43.7 years for females and 49.6 years for males. In contrast, the Wang & Young (2004) paper had a smaller patient pool of 13 participants, with a mean age of 27 years, which may account for the variance between the studies.

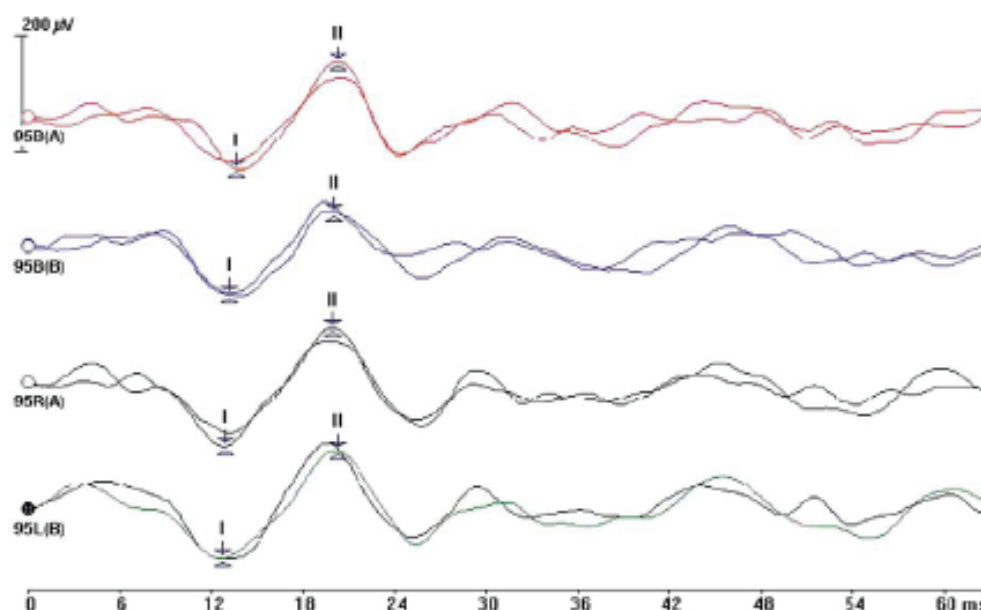


Figure 1.6. Normal VEMP response with the initial positive peak (P1) and negative peaks (N1) (Wang & Young, 2003).

1.3.1. Stimulus Characteristics

The cervical VEMP relies on acoustic stimulation of single SCM motor units which results in an initial inhibition of projecting neurons. Activation of these units however, is not synchronous and consequently is best recorded by averaging unrectified EMG (Colebatch & Rothwell, 2004). Numerous researchers have used a 500 Hz tone burst as the preferred method of stimulation as lower stimulus intensities are required to elicit a response compared to clicks (Welgampola & Colebatch, 2005) and Rauch et al. 2004b found it to be the most optimal frequency to elicit a response. A tone burst with a 1 ms rise and fall time and 2 ms plateau is commonly applied at an intensity of at least 95 dB SPL (Rauch et al., 2004b; Kuo, Yang, & Young, 2005; Chen & Young, 2006; Young, Wu, & Wu, 2002; Wang & Young, 2004; Young & Kuo, 2004; Young, Huang, & Cheng, 2008; Sheykholeslami, Murofushi, & Kaga, 2001; Chang, Yang, Wang, & Young, 2007). An intensity of 95 dB SPL is required for adequate stimulation of the vestibular apparatus for the acquisition of a repeatable response (Welgampola & Colebatch, 2005). Presentation of intensities greater than this value was not shown to change the response rate nor the latency of the p13 n23 waveform. The intensity does however affect the amplitude of this response. An increase in the amplitude of the p13 n23 response was seen when the stimulus intensity increased from 95 dB SPL to 105 dB SPL (Wang & Young, 2004). Furthermore, a significant decrease in response rate (Wang & Young,

2004) and amplitude (Zhou & Cox, 2004) has been reported with a drop in intensity level from 95 dB SPL to 85 dB SPL and then again to 75 dB SPL. As a result, the threshold in which the lowest acoustic stimulus will produce a response is between 85-90 dB SPL (Bath et al., 1998; Colebatch et al., 1994).

1.3.2. Presentation of Acoustic Stimuli

The VEMP response is largely an ipsilateral response with greater amplitude on the ipsilateral ear compared to the contralateral ear (Colebatch et al., 1994). Monaural presentation of the acoustic stimulus rather than binaural presentation is also the most adopted method for obtaining the VEMP response. Wang and Young (2004) and Wang and Young (2003) demonstrated that while there was no significant difference between monaural and binaural presentation for latency and threshold there was a significant decrease in the amplitude of the waveform when the stimuli were presented to both ears.

1.3.3. Dependence on EMG

The mean amplitude of the signal differs greatly between studies as it varies with the tonic EMG level (Zhou & Cox, 2004; Akin, Murnane, Panus, Caruthers, Wilkinson, & Proffitt, 2004). The most common and preferred subject position applied by researchers is the supine position with the head slightly raised rather than the upright position (Sheykholeslami et al., 2001; Welgampola & Colebatch, 2005; Patko, Vibert, Huy, & de Waele, 2003).

1.3.4. Electrode Placement

Electrode position is another variable in recording the cervical VEMP. Sheykholeslami et al. (2001) sought to determine the optimal electrode sites for obtaining the p13 n23 response. Results from the study concluded that active electrodes placed over either the upper or middle portion of the SCM produced the largest waveforms and, furthermore positioning over the middle SCM produced the most reliable and clear waveforms. Placement of the indifferent and earth electrodes was on the upper sternum and the area between the eyes, respectively. With the exception of the earth location, many following studies adopted this electrode configuration (Basta et al., 2005; Monobe & Murofuchi, 2004; Sheykholeslami & Kaga, 2002). Although the indifferent electrode location also varies, a majority of the studies still place the active electrodes over the upper half of the SCM (Young et al., 2002; Chen & Young, 2006; Ribeiro,

de Almeida, Caovilla, & Gananca, 2005; Kuo, Yang, & Young, 2005; Rauch et al., 2004b; Wang & Young, 2004; Young & Kuo, 2004; Zhou & Cox, 2004).

1.3.5. Effect of Age and Gender

The effect of age and gender has also been researched as a further variable in the acquisition of the cervical VEMP response. Although no significant effect of gender was seen in the study by Basta et al. (2005) nor the Ochi and Ohashi (2003) study, results from the Ochi and Ohashi (2003) study, Welgampola and Colebatch (2001) and Su, Huang, and Cheng (2004) study concluded that there is a significant difference between the age of the participant and the amplitude of the first positive and negative peaks of the VEMP response. Notably a decrease in amplitude was seen with an increase in age and correspondingly an increase in threshold was needed to obtain the response. In contrast, the Basta et al. (2005) and Su et al. (2004) studies found no significant effect of age on the latencies of the VEMP response. The study by Lee, Cha, Jung, Park, & Yeo, (2008) (n = 97) determined a prolongation of p13 and n23 with age however. In conclusion, the amplitude of the VEMP response may be altered as age increases which may be due to degeneration of the otoconia (Johnsson & Hawkins, 1972), a decrease in the number of vestibular afferents (Bergstrom, 1973) or a loss of hair cells (Rosenhall, 1973). Finally, for the optimisation of the VEMP response transmission of the acoustic stimulus to the vestibular system must not be hindered. Therefore, in patients with known conductive hearing losses, due to disruption of the middle ear, the intensity of stimulation at the level of the saccule may compromise the response (Colebatch et al., 1994).

Analysis of the VEMP response involves the measurement and relative comparison of the latency and amplitude of the p13 and n23 peaks. In addition the interaural amplitude difference (IAD) ratio is also widely used in the assessment of the VEMP. Calculation of the IAD involves comparing the amplitude difference between the first positive and negative peaks in both ears and dividing this amount by the sum of the first positive and negative peaks for both ears. The study by Wang and Young (2003) considered an IAD ratio of 0.13 ms within normal limits however an IAD of 0.33 ms or more was regarded abnormal.

1.4. Ménière's Disease

Ménière's disease is a progressive idiopathic disease which can result in degeneration of the hair cells in the saccule and cochlea. It was first described in 1861 by Prosper Ménière has been noted as the most common disease of the vestibular system (Minor, Schessel, & Carey, 2004). Published prevalences, as shown in Table 1.1, of the disease across the globe differ.

Table 1.1. Prevalence rates of Ménière's disease for reported for Japan, Finland and the United States of America.

Region		Prevalence	Reference
United States		218.2 per 100,000	Wladislavosky-Waserman, Facer, Mokri, & Kurland (1984)
Finland		513 per 100,000	Havia, Kentala, & Pyykko (2005)
Japan	Hida	36.6 per 100,000	Shojaku, Watanabe, Fujisaka, Tsubota, Kobayashi, Yasmura, & Mizukoshi (2005)
	Nishikubiki	21.4 per 100,000	Shojaku, Watanabe, Fujisaka, Tsubota, Kobayashi, Yasmura, & Mizukoshi (2005)

The difference amongst studies could be attributed to the complex nature of the disease. Ménière's disease is characterized by a fluctuating, progressive hearing loss and episodic vertigo which can alter the true prevalence of these key symptoms at the time of diagnosis.

Ménière's disease is characterized by four symptoms which include; fluctuating hearing loss, tinnitus, vertigo and aural fullness. For a diagnosis of "definite Ménière's disease" the patient must satisfy the criteria set by the Committee on Hearing and Equilibrium (1995) shown below in Table 1.2. Another method for diagnosing Ménière's disease is the 10-point scoring system by Gibson (1990) as shown in Table 1.3. A minority of studies in the literature have included participants without clinically certain diagnosis of Ménière's disease in their samples (Chen & Young, 2006; Thomas & Harrison, 1971). In this classification "Certain" Ménière's disease is defined as definite plus histopathologic confirmation of hydrops, which required post-mortem. Currently the definition does not recognize any electrophysiologic test which can confirm the presence of hydrops in a living (anti-mortem) patient.

Table 1.2. Clinical criteria of Ménière's disease (Committee on Hearing and Equilibrium, 1995)

Diagnostic Scale	Clinical Criteria
Certain Ménière's	Definite Ménière's, plus histopathologic confirmation
Definite Ménière's	Two or more definitive spontaneous episodes of vertigo lasting 20 minutes or longer Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Probable Ménière's	One definite episode of vertigo Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Possible Ménière's	Episodic vertigo of the Ménière type without documented hearing loss, or Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes Other causes excluded

Table 1.3. This table is from Gibson (1990) for diagnosis of Ménière's disease using a ten-point score based on the patients symptoms.

Please answer the question of each of the following questions: "Have you ever had....?"		
Vertigo	Rotational vertigo	1
	Attacks of rotational vertigo > 10 min	1
	Rotational vertigo associated/linked with one or more of H, T, P.	1
Hearing	Sensorineural hearing loss	1
	Fluctuating hearing loss	1
	Hearing loss or fluctuation associated/linked with one or more of H, T, P.	1
Tinnitus	Peripheral tinnitus lasting > 5 min	1
	Tinnitus fluctuating or changing with one or more of V, H, P.	1
Pressure	Constant aural pressure lasting > 5 min	1
	Pressure fluctuating or changing with one or more of V, H, T.	1
Maximum score adds to 10		

Unfortunately, the etiology of Ménière's disease remains controversial. Some researchers claim that the symptoms of Ménière's disease are a result of viral vestibular ganglionitis (Gacek & Gacek, 2001), trauma (Paparella & Mancini, 1983) and genetic predisposition (Paparella & Djalilian, 2002). Other researchers suspect pathologies in the stria vascularis may be responsible (Masutani, Takahashi, & Sando, 1991), or possibly autoimmune conditions (Ruckenstein, 1999). Evidence has also indicated that patients with Ménière's disease have a significantly higher prevalence of allergies compared to the general population (Derebery & Berliner, 2000). It is probable that the onset of Ménière's disease is a result of multiple insults to the inner ear labyrinth (Ruckenstein, 1999; Paparella & Djalilian, 2002). Evidence from post mortem temporal bone studies suggest that the symptoms characteristic of Ménière's disease are due to an increase in endolymph volume in the membranous labyrinth of the vestibule and cochlea, visible histologically as distention of the saccule and/or including the cochlea.

In temporal bone studies the most common finding is endolymphatic hydrops whose aetiology is unknown. Endolymph, produced by the stria vascularis and the dark cells of the vestibular system, has a high concentration of potassium in contrast to perilymph, which has a high concentration of sodium. The endolymph flows throughout the entire vestibular system and cochlea, and is regulated in its composition by the endolymphatic sac. Endolymphatic hydrops causes distention of the endolymphatic sac and the endolymphatic components of the vestibular system and cochlea. This increase in volume of endolymph causes pressure to build up at the connecting duct between the cochlear and vestibular labyrinth. This results in displacement of structures in the cochlea, leading to a hearing loss (Baloh & Honrubia, 2001). It has been suggested that a pathologic change in the cells of Reissner's membrane can be identified as a result of endolymphatic hydrops and in particular in patients with Ménière's disease. Significantly the epithelial cells of Reissner's membrane were irregular in spacing and there was a reduction in the number of mesothelial cells. Furthermore, an increasing number of epithelial cells were found in the temporal bones with Ménière's disease. This number increased with the progression of the disease in contrast to a decrease in the number of these cells with age in controls (Cureoglu, Schachern, Paul, Paparella, & Singh, 2004). This provides further evidence for the presence of endolymphatic hydrops in this disease and may provide evidence for the pathophysiology of the disease. However it is unclear whether Ménière's disease is a consequence of endolymphatic hydrops or if endolymphatic hydrops indeed presents itself after Ménière's disease has been established.

A consequence of endolymphatic hydrops is depression of the basilar membrane and saccular wall into the perilymphatic space. This change in displacement results in a hearing loss particularly at the lower end of the frequency range (Xenellis, Linthicum, Webster, & Lopez, 2004). Therefore, the key symptom of Ménière's disease is a low frequency hearing loss. Distention of the vestibular apparatus has been proposed to cause the second key symptom, vertigo attacks. No conclusive evidence exists as to why the vertigo and hearing loss symptoms fluctuate. However, research indicates that an irreversible collapse of Reissner's membrane in the cochlea results in the permanent hearing loss seen in the latest stages of the disease (Young et al., 2008).

The onset of Ménière's disease can present as just one symptom or a combination of presenting symptoms. For example Havia, Kentala, & Pyykko (2002) observed a predominance of patients who noticed the three signifying symptoms including, hearing loss, tinnitus and

vertigo at the onset of the disease. The mean age of onset of the Ménière's symptoms is shown in Table 1.4.

Table 1.4. This table indicates the mean age of onset of Ménière's disease symptoms.

Reference	Mean age of onset of Ménière's symptoms
Havia and Kentala (2004)	44 years n=243
Havia et al. (2002)	44 years n=242
Chaves, Boari, and Munboz (2007)	42.9 years (n=39)
Thomas & Harrison (1971)	50-54 years (n=183).

The range of age of onset was found to be as young as 17 years and as old as 79 years (Havia & Kentala, 2004). No difference between genders exists for the duration, intensity nor frequency of vertigo attacks as described by Havia and Kentala (2004).

Ménière's disease is dominantly unilateral with bilateral cases occurring only 16% of the time (Havia & Kentala, 2004). Furthermore, there is no predominance of one ear compared to the other. For example, Havia and Kentala (2004) determined that the affected ear was left sided in 46% and right sided in 35% (n=205). Bilateral cases are expected to have the same progression of symptoms as unilateral cases; however they are more likely to seek medical advice earlier than patients who only have one affected ear (Chaves et al., 2007). The likelihood of bilateral disease increases with the progression of unilateral Ménière's disease (Havia & Kentala, 2004).

Hearing loss is one of the criteria set by the Committee on Hearing and Equilibrium (1995) for the diagnosis of Ménière's disease. Patients with the disease can present with hearing loss in either ear or bilaterally. Participants in the Havia et al. (2002) study who suffered from bilateral Ménière's disease had significantly reduced hearing thresholds and a longer history of presenting symptoms than participants who only had one diseased ear. It is well documented that the hearing loss associated with the disease progressively gets worse over time (Havia et al., 2002; Thomas & Harrison, 1971). Initially thresholds as low as 20 dB HL can be coupled

with the onset of the disease. These thresholds can progress to a hearing loss as great as a severe to profound hearing loss. The most common audiogram configuration in patients with Ménière's disease was a flat hearing loss (47.6%) followed by a gently downward sloping hearing loss. Only 12.2% of audiograms analysed demonstrated a rising hearing loss (Thomas & Harrison, 1971). In conjunction with the progressive nature of the hearing loss, the loss can also fluctuate over time. For example Havia et al. (2002) reported that 44% of participants experienced a fluctuation in their thresholds. A worsening in the participants hearing levels was reported in 55% during an attack of vertigo (Havia et al., 2002). The progression of the disease is summarized into four stages based on the puretone average (PTA) audiometric threshold at 0.5, 1, 2, and 3 kHz presented in Table 1.5.

Table 1.5. Progression of Ménière's disease staged by pure-tone averaging (Committee on Hearing and Equilibrium Guidelines for the Diagnosis of Ménière's Disease, 1995).

Stages of Ménière's disease	Pure-tone average audiometric thresholds at 0.5, 1, 2, and 3 kHz
Stage I	Less than 25 dB HL
Stage II	26-40 dB HL
Stage III	41-70 dB HL
Stage IV	Greater than 70 dB HL

Probably the most debilitating symptom of Ménière's disease is vertigo. Vertigo is characterised by a sensation of movement. Attacks of vertigo vary in frequency and duration, with some attacks lasting as short as a few seconds and as long as a few days (Havia & Kentala, 2004). Most commonly the attacks last less than one day (88%) and as a result of these attacks patients may be bed-ridden and nauseous. The frequency of vertigo is most commonly once a month (63%) whilst continuous vertigo was seen in 5% of participants. The likelihood of continuous vertigo increased with prolonged duration of Ménière's disease. Furthermore, the duration and severity of the attacks also increased with the prolongation of the disease (Havia & Kentala, 2004). Neither the frequency, duration nor intensity of vertigo attacks is correlated with the degree of hearing loss (Havia et al., 2002).

Patients with Ménière's disease suffer from tinnitus which often presents as a low frequency sound (Vernon, Johnson, & Schleuning, 1980). The intensity and severity of tinnitus increases with hearing loss, and is more pronounced in participants who suffer from the disease in both ears (Havia et al., 2002). Furthermore, patients who presented with symptoms earlier in life were more likely to present with severe tinnitus. Whilst tinnitus is correlated to the deterioration in hearing thresholds it is not related to vertigo attacks (Havia et al., 2002). However participants with more severe tinnitus were more likely to have Tumarkin drop attacks¹, motor difficulties and balance disturbance (Havia et al., 2002).

As described below, electrocochleography (ECochG) and vestibular evoked myogenic potentials (VEMPs) are other diagnostic measures which can be used in the battery of tests for Ménière's disease.

1.4.1. Electrocochleography and Ménière's Disease

Electrocochleography (ECochG) has been used as a clinical tool to diagnose Ménière's disease. ECochG involves the placement of an electrode near the round window or on the promontory. The anatomical position of the round window allows for recordings of the cochlear microphonic (CM), summing potential (SP) and action potential (AP) within the cochlea. The cochlear microphonic is a product of OHC function whilst the summing potential and action potential are products of IHC function.

Three different methods of obtaining an ECochG exist, namely transtympanic; where the electrode is punctured through the tympanic membrane and rests upon the promontory or round window, extratympanic; where the electrode is placed in the ear canal, and tympanic; where the electrode is placed up against the tympanic membrane. The sensitivity of each method depends entirely on the signal to noise ratio of the environment. For instance the signal of interest can be as small as 10 μ V whilst environmental noise may be hundreds of times larger (Sass, Densert, & Arlinger, 1998). Thus transtympanic ECochG, where the signal to noise ratio is largest, is the most sensitive placement for recording.

¹ Tumarkin first described a sudden fall as a result of an otolithic organ in 1936. This type of fall occurs most commonly in patients whom have had endolymphatic hydrops for a prolonged period (Tumarkin, 1936). 5-10% of patients with Ménière's disease experience these attacks due to a strong stimulation of an otolith (Baloh, Jacobson, & Winder, 1990).

Ménière's disease results in displacement of the basilar membrane due to endolymphatic hydrops of the cochlea in particular the scala tympani. This results in an asymmetric vibration of the basilar membrane (Gibson & Arenberg, 1990) and distorts the baseline CM as the hair cells are displaced (Gibson, 1996). The alternating stimulus nulls the CM and the resultant DC potential is now dependant on the distorted baseline. As a result an increase the negativity of the SP value and thus the SP/AP ratio is observed (Gibson, 1996).

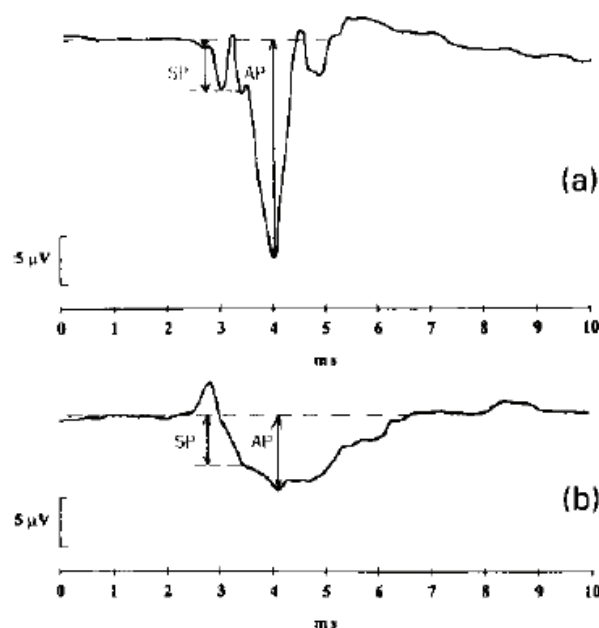


Figure 1.7. An electrocochleographic response from a participant with normal hearing (a) and from a participant with Ménière's disease (b). This diagram indicates a significant reduction in the action potential (AP) amplitude and an enlargement of the SP amplitude from the Ménière waveform compared to the normal waveform. (Sass et al., 1998)

The SP/AP ratio is widely used for the diagnosis of endolymphatic hydrops where basically the SP amplitude is divided by the AP amplitude. A SP/AP ratio of 0.33 or more (Gibson, Prasher, & Kilkenny, 1983; Arenberg, Gibson, Hohmann, & Mihalco, 1992) is considered indicative of endolymphatic hydrops. Studies by Gibson, Moffat, and Ramsden (1977), Sass et al. (1998), Conlon and Gibson (2000) and Gibson (1996) amongst others, have indicated a significant difference in the SP/AP ratio between participants with Ménière's disease compared to controls as seen in Figure 1.7. The advantage of taking into account the AP amplitude is to compensate for a potential loss of hair cells as a result of Ménière's disease (Gibson, 1996). Normative ECoChG data performed with tone burst stimuli is shown in Table 1.6. For example,

an SP amplitude greater than $-2 \mu\text{V}$ is considered abnormal, for a 500 Hz tone burst at 75 dBHL, for a patient with a hearing loss less than 25 dB HL at this frequency.

Table 1.6. This table represents the norms for tone burst ECoG summating potential (SP) (Gibson, 1992)

Tone burst Frequency	Hearing level dBHL	Abnormal if SP >
.5 kHz (75 dBHL)	Under 25	$-2 \mu\text{V}$
	20 – 35	$-2 \mu\text{V}$
	40 – 55	$-2 \mu\text{V}$
	60 – 75	$-1 \mu\text{V}$
1 kHz (90 dBHL)	Under 25	$-6 \mu\text{V}$
	20 – 35	$-6 \mu\text{V}$
	40 – 55	$-6 \mu\text{V}$
	60 – 75	$-3 \mu\text{V}$
2 kHz (100 dBHL)	Under 25	$-9 \mu\text{V}$
	20 – 35	$-7 \mu\text{V}$
	40 – 55	$-5 \mu\text{V}$
	60 - 75	$-5 \mu\text{V}$
4 kHz (75 dBHL)	Under 25	$-9 \mu\text{V}$
	20 – 35	$-5 \mu\text{V}$
	40 – 55	$-5 \mu\text{V}$
	60 – 75	$-5 \mu\text{V}$

1.5. Ménière's Disease and Cervical Vestibular Evoked Myogenic Potentials

Cervical vestibular evoked myogenic potentials (cVEMPs) have been used as part of the test battery for Ménière's disease (Colebatch et al., 1994; Bath et al., 1998; Rauch et al., 2004b). The cVEMP waveform of patients with vestibular disorders, such as Ménière's disease, show latency, amplitude and threshold differences compared to controls. In addition, cVEMP abnormalities are seen half of all participants with Ménière's disease in the study by Ribeiro et

al 2005 (50%), de Waele et al. 1999 (54%), and Kuo et al. 2005 (67%). Threshold shifts and altered tuning have also been observed in patients with Ménière's disease when compared to controls (Lin et al, 2006; Rauch et al. 2004b). This is likely to be attributed to pathology of the saccule, in particular saccular hydrops, suggested by Rauch et al. (2004b). However the overall lack of sensitivity of the cVEMP may be attributed to the fact that the hydrops associated with Ménière's does not exclusively affect the saccule.

In patients with Ménière's disease the latency of the initial positive and negative peaks is unlikely to change as saccular hydrops does not affect electrical or acoustic transmission (Rauch et al. 2004b). For example, Osei-Lah, Ceranic, and Luxon (2008) did not determine any statistical difference between the control and Ménière groups for the P1 and N1 latency measures nor did the de Waele, Huy, Diard, Freyss, and Vidal (1999) or Young, Huang, & Cheng, (2003) studies. Similarly, the Ribeiro et al. (2005) and Akkuzu, Akkuzu, and Ozluoglu (2006) studies indicated an increase in latency of the first positive peak in only 10% of participants.

Research suggests that the amplitude and threshold are more likely to be altered in patients with Ménière's disease. Rauch et al. (2004b), Rauch et al. (2004b), Ohki, Matsuzaki, Sugawara, & Murofushi, (2002), Akkuzu et al. (2006) and Murofushi et al. (2001), Chen & Young (2006) all found a statistically significant reduction in amplitude of the response in Ménière's ears. In addition, Lin, Timmer, Oriel, Zhou, Guinan, Kujawa, Herrmann, Merchant, & Rauch (2006) and Rauch et al. (2004b) found an increase in threshold in the symptomatic and asymptomatic ears compared to controls for the cervical VEMP. However, the Osei-Lah et al. (2008) study did not find any statistically significant differences between the control and Ménière groups at threshold.

The IAD ratio is another method that has been shown to distinguish between control and Ménière participants. The Osei-Lah et al. (2008) study applied this IAD ratio to the Ménière groups in their study and found a significant difference between these and the control group. The Young et al. (2003) investigated the IAD ratio for its ability to stage Ménière's disease. The study determined that an increase in IAD ratio is likely to represent a higher stage of the disease. For example, they revealed an IAD ratio of -0.02 ± 0.20 in stage I ears and an IAD ratio of -0.54 ± 0.43 in stage IV Ménière's diseased ears. The results from the Osei-Lah et al. (2008) study did not reach statistical difference between the stages of Ménière's disease in

contrast to this study however. The authors proposed that this was likely due to the small sample size of the Ménière groups ($n=11$ and $n=9$).

1.6. Vestibulo-ocular Reflex Pathway

Similar to the vestibulo-collic pathway the vestibulo-ocular reflex (VOR) pathway originates in the vestibular system and terminates onto motor nuclei. In contrast this pathway extends to the ocular muscles of the eye which can also be activated by acoustic stimuli (Jombik & Bahlyl, 2005). The role of the VOR is the maintenance of eye gaze in the presence of head movement (Jombik & Bahlyl, 2005). The saccule in particular responds to vertical changes in linear acceleration of the head due to the relative movement of the otoconia over the stereocilia of the saccule. This is possible due to the vertical arrangement of its macula. This selective stimulation of the saccule is via the sacculo-ocular reflex pathway and can be achieved by using air conduction stimuli rather than bone conduction stimuli (Young, Fernandez, & Goldberg, 1977; Murofushi & Curthoys, 1997). Bone-conduction stimuli has been proposed to result in saccular and utricular activation (Todd et al., 2007).

Studies by Aw, Todd, Aw, Magnussen, Curthoys, and Halmagyi (2006), Zhou, Mustain, and Simpson (2004), and Jombik and Bahlyl (2005) have indicated the presence of eye movement in response to acoustical stimulation of the vestibular system in both animal and human studies. Investigations by Welgampola, Migliaccio, Myrie, Minor, & Carey (2008) suggest that the time lapse between eye movement onset and the oVEMP onset is as large as 5.4 ms. This result indicates that the oVEMP is not an electro retinal potential but rather a response which contributes to sound-evoked eye movements Welgampola et al. (2008). In addition, results from this study suggest that acoustic stimulation of the otoliths results in the oVEMP.

The reflex pathway for air conduction stimuli for the oVEMP is not entirely understood. It is likely that this type of stimulation activates a similar pathway to that of the transverse vestibular ocular reflex pathway (Todd et al., 2007). The proposed VOR pathway involves acoustic stimulation of the saccule, which can be mimicked by electrical stimulation, which in turn recruits saccular nerve afferents due to the transduction pathway described earlier. The saccular afferents merge to form saccular nerve which merges again into the vestibular nerve (Isu, Graf, Sato, Kushiro, Zakir, Imagawa, & Uchino, 2000). The vestibular nerve passes through the internal auditory canal to form the vestibular tract. This tract then terminates on the vestibular nuclei in the medulla oblongata in the brainstem. There are two sets of four

vestibular nuclei which lie on either side of the brainstem, namely the superior vestibular nucleus, the lateral vestibular nucleus, medial vestibular nucleus and the descending vestibular nucleus (Baloh & Honrubia, 2001). The vestibular nuclei send ascending impulses to the oculomotor nuclei of the eye, cerebellum, cortex and hypothalamus amongst others. This VOR pathway is a three neuron arc by which the first neuron from the vestibular nerve, the second is an interneuron which terminates on the abducens nucleus and the third is the ocular motoneuron (Furman & Cass, 2003). This three-neuron arc can be concluded due to the small latency of the VOR which typically lies between 2.3 to 3.3 ms. Furthermore, we can propose that this pathway is likely to be disynaptic (Isu et al., 2000). Activation of oculomotor nuclei results in excitatory input to the ipsilateral and contralateral superior rectus muscle, the contralateral superior oblique and ipsilateral inferior rectus muscles. Inhibitory activation of the ipsilateral and contralateral inferior recti oculomotor nuclei also occur. Excitation and inhibition of corresponding oculomotor nuclei results in contraction and relaxation of the eye muscles resulting in coordinated eye movements due to a change in head position as depicted in Figure 1.8. In addition, the crossed nature of the projections results in stronger contralateral responses with ocular VEMP testing in contrast to the cervical VEMP.

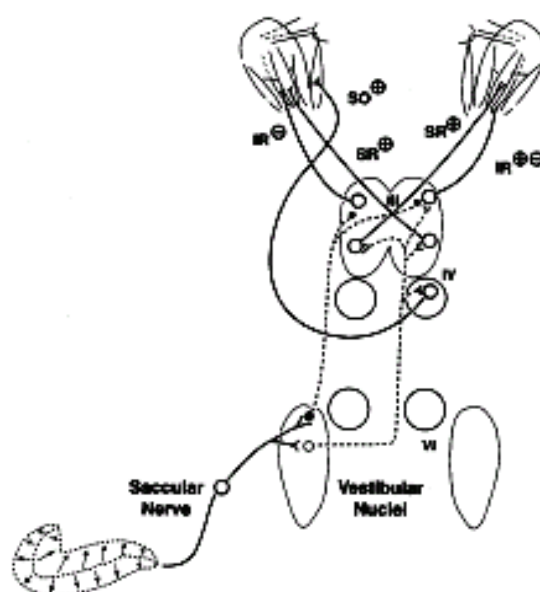


Figure 1.8. The sacculo-ocular reflex pathway. Saccular nerve projections from the saccule excite and inhibit vestibular nuclei. Post-synaptic potentials produced travel to the oculomotor nucleus and trochlear nucleus. Multiple synapses occur at the level of the oculomotor nucleus. Inhibitory post-synaptic potentials synapse on the ipsilateral and contralateral inferior recti motoneurons; whilst excitatory potentials stimulate the ipsilateral and contralateral superior rectus, contralateral superior oblique and the contralateral inferior rectus oculomotor nuclei. Stimulation of these motoneurons results in stimulation of the extraocular muscles (Isu et al., 2000).

Evidence of electrical stimulation of the saccular nerve by Isu et al. (2000), resulted in a small waveform which increased in amplitude with an increase stimulus intensity which provides evidence that additional nerve fibres are recruited at higher levels. A plateau was eventually reached representing that the maximum amount of saccular afferents was recruited at this point. Interestingly, analysis of the superior and inferior recti motoneurons indicated that only 30% were activated by saccular-nerve stimulation. Compared to the number of utricular projections this percentage is considerably reduced (Isu et al., 2000).

In the analysis of the latency and amplitude of the extraocular EMG activity contributions from distant neural activity in the body, blinking and eye movement has the potential to affect the oVEMP response. Todd et al. (2007) stated that neural contributions from distant sources from the skull can be cancelled when active electrodes are situated within close proximity, furthermore artefact rejection windows can be utilized in to exclude blink artifacts. In addition, the latency of eye movement occurs at a significant period after extraocular activity (Todd et al., 2007; Welgampola et al., (2008) thus exclusion of eye movement, blink artefact and distant neural activity can be achieved. Similar to the vestibulo-collic reflex pathway the vestibulo-ocular reflex pathway has also been shown to degenerate with age. Kerber, Ishiyama, and Baloh (2006) determined that not only the VOR but also the visual-vestibulo-ocular reflex demonstrated a significant age related decline in function. Furthermore, Clark and Isenberg (2001) identified a decrease in gaze comparative to age for movements of the eye including elevation, adduction, abduction and, least of all, depression. It may be possible that the reflex pathway from the saccule to the eyes has a similar fate with age as the VOR pathway.

1.6.1. Ocular Vestibular Evoked Myogenic Potentials

Recent studies by Rosengren et al. (2005), Chihara et al. (2007) and Todd et al. (2007) indicated the presence of an ocular vestibular evoked myogenic potential (oVEMP). Similar to the cVEMP the oVEMP requires acoustic stimulation of the saccule, which transfers into a measureable myogenic response by recording EMG activity over the ocular muscles. Initially, Rosengren et al. (2005) applied bone conduction stimuli to elicit the response however, air conduction stimuli and head accelerations have also been effective in producing this evoked potential (Todd et al., 2008; Todd et al., 2007).

The response obtained is unlikely to be attributed to eye movement as the ocular VEMP occurs 3 ms before its onset (Todd et al., 2007). Similar to the cervical VEMP, the ocular VEMP has a vestibular (saccular) reflex pathway, although this pathway terminates at the ocular motor nuclei. The latency of the initial negative peak suggests that the pathway is oligosynaptic and not polysynaptic in character (Chihara et al., 2007). In addition, the response is an excitatory response in contrast to the cervical VEMP response.

Placement of electrodes over the inferior oblique muscle directly inferior to the eye has been found to produce the largest response, after comparisons between the superior and inferior recti and oblique muscles (Todd et al., 2007). Due to the positioning of the electrodes over the inferior oblique muscle the direction of the participants eye gaze has been shown to alter the oVEMP response. Evidence from Rosengren et al. (2005) and Chihara et al. (2007) suggest that the optimal gaze direction for the response is superomedial in direction, bringing the belly of the inferior oblique muscle closer to the skins surface.

Contralateral stimulation results in larger amplitudes of the oVEMP response as the sacculo-ocular pathway is likely to be crossed in nature (Todd et al., 2007; Isu et al., 2000). This is in contrast to the cVEMP which is largely an ipsilateral response. Acquisition of the oVEMP is more likely to occur with a short tone burst stimulus compared to a click stimulus. For example, the study by Chihara et al. (2007) determined a 90% response rate with short tone bursts compared to 50% with clicks. They suggested that this was likely due to the fact that the short tone burst with a period of 4 ms produces considerably more energy than a 0.1 ms click. In addition, the tone burst frequency of 500 Hz is more likely to be specific in targeting a response from the saccule as previously discussed in the cervical VEMP section 1.3. Furthermore, the threshold of the click evoked oVEMP was found to be higher than with a tone burst stimulus (Chihara et al., 2007).

The ocular VEMP has the advantage over the cVEMP in that participants and patients do not have to maintain activation of their neck muscles. This will be of more use when assessing the geriatric and infant patients. Iwasaki, Smulders, Burgess, McGarvie, MacDougall, Halmagyi, Curthoys (2008) briefly discussed the difficulty elderly have maintaining activation of their SCM. In addition, Maes, Vinck, De Vel, D'haenens, Bockstael, Keppler, Phillips, Swinnen, & Dhooge (2009) suggested that a small proportion of their participants found the cervical VEMP

strenuous whilst the Wang et al. (2009) found that their participants found the oVEMP particularly easy to perform.

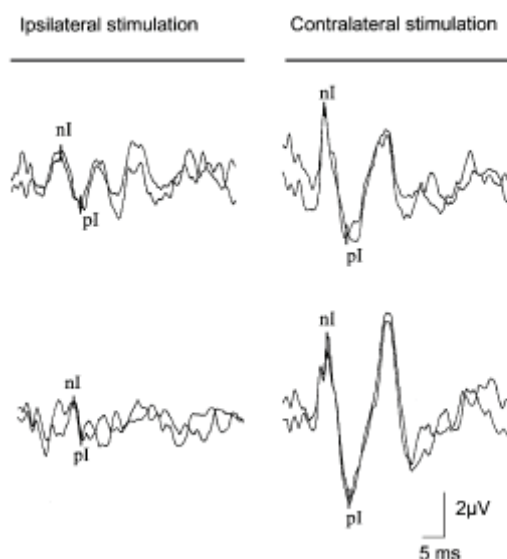


Figure 1.9. This diagram depicts the oVEMP response from both ipsilateral and contralateral stimulation with a 500 Hz 135 dB SPL tone burst (Chihara et al., 2007).

The study by Iwasaki et al. (2008) revealed an absence of the first N1 peak in patients with no vestibular function. However, the response was preserved in patients with a sensorineural hearing loss, suggesting that the oVEMP is dependent on vestibular integrity. Rosengren et al. (2005) also revealed that the oVEMP response was absent in patients with no vestibular function. Owing to this idea the oVEMP test has been applied to a variety of vestibular pathologies including vestibular neuritis, delayed endolymphatic hydrops, Ménière's disease and superior canal dehiscence (Chihara et al., 2007; Halmagyi, McGarvie, Aw, Yavor, & Todd, 2003). For example, participants with superior canal dehiscence had significantly larger oVEMP amplitudes compared to controls (Halmagyi et al., 2003). The study by Chihara et al. 2007 utilised the ocular VEMP test on three participants with Ménière's disease. A 500 Hz tone burst (135 dB SPL) was presented to symptomatic ear, and two of the three participants exhibited a depressed or absent response.

Results from the Welgampola, et al. (2008) study determined a mean latency of the n1 and p1 peaks to be 11.9 ± 0.1 ms and 17.8 ± 0.6 ms, respectively with an air-conducted stimulus. In addition, the amplitude of the contralateral eye (6.25 ± 1.03 μ V) to the stimulus was four times larger than the ipsilateral eye (1.89 ± 0.57 μ V). The latency of the n1 and p1 peaks from the Chihara et al. (2009) study was 11.0 ± 0.8 ms and 16.0 ± 1.3 ms, respectively. The peak-to-

peak amplitude between n1p1 was 7.7 ± 7.5 V. The typical waveform is shown in Figure 1.9. Similar to the cervical VEMP response the latency increases and the amplitude decreases with age (Iwasaki et al., 2008).

The effect of stimulus polarity has not been investigated to our knowledge. The Iwasaki et al. (2008) study attempted to investigate both the rarefaction and condensation stimuli with a BC stimulus but a mechanical delay with the rarefaction stimulus was apparent and thus excluded.

1.7. Aims of the Proposed Study

Clinicians who have used cervical VEMP testing have found it useful in diagnosing Ménière's disease (Lin et al., 2006; de Waele et al., 1999; Rauch et al., 2004b; Rauch et al., 2004a; Kuo et al., 2005). Furthermore, cVEMPs are useful in staging the disease (Young et al., 2003). By comparing the ocular and cervical VEMP tests this study can investigate the ability of the ocular VEMPs to “stage” Ménière's disease. The study benefits from having a pool of participants with “clinically certain” Ménière's disease – something which is not consistently controlled for in the literature for example the Cheng and Young (2006) and Osei-Lah et al. (2008) studies. In addition to determining a new diagnostic method for Ménière's disease we hope that the new ocular VEMP will improve the number of possible patients in the population who can receive vestibular testing in this manner. Cervical VEMP testing requires strenuous activation of the SCM by lifting the head from a supine position. Instead we hope that activation of the inferior oblique muscle of the eye by looking supereomedially is easier to perform and maintain. We hope that when this technique is applied to the geriatric and infantile populations that reliable responses are obtained more effortlessly.

To achieve this, the study will compare the latencies, amplitudes and interaural amplitude differences between the cervical and ocular VEMP data between control participants and those with Ménière's disease. In addition, we will investigate the threshold of the cervical and ocular VEMPs between these patient groups. We hoped to investigate each of the four stages of Ménière's disease with these measures. However, owing to the small sample size, we had to group stages 1 and 2 into an ‘early Ménière group’ and stages 3 and 4 into a ‘late Ménière group’.

CHAPTER TWO

METHODS

2. Method

To determine the sensitivity of ocular VEMP testing in comparison to cervical VEMP testing, evoked potentials in the ocular and cervical muscles were analysed. More specifically, the threshold, latency, amplitude and interaural amplitude ratios of the two types of VEMP test were investigated and compared. Participants were divided into two groups. The first was a control group of participants with no known vestibular pathologies. The second was a patient group with “clinically certain” Ménière’s disease, in that endolymphatic hydrops confirmed with ECoHG. Collected data from the patient group was analysed in groups according to the pure tone audiometry results in an attempt to determine the ability of both ocular and cervical VEMPs to stage Ménière’s disease. The study was approved by the Health and Disability Upper Regional A Ethics Committee (ref: URA/08/04/030) and the University of Canterbury Human Ethics Committee (ref: HEC 2008/61). Furthermore, the questionnaire received low risk ethics approval by the University of Canterbury Ethics Committee (ref: HEC 2009/LR/05). The instrumentation, participant characteristics and the procedures used in this study are discussed below.

2.1. Participants

22 adult control participants between the ages of 22 and 63 (mean age of 34.3 ± 13.3 years) recruited voluntarily from the University of Canterbury took part in the study. All control participants resided in the wider Canterbury region. An initial pool of participants ($n = 23$) were analysed via tympanometry and audiometry. The participants in this control group will be referred as n1 to n22 for individual identification throughout this study. 22 control participants (female 13/male 9) remained after excluding a subject who met one or more of the following criteria:

1. a significant history of balance or vertigo problems.
2. a conductive hearing loss, determined by either pure tone audiometry or tympanometry.
3. inability to maintain tonic EMG neck activity by raising their head from a supine position
4. inability to maintain eye gaze in the superomedial direction.

Figure 2.1 shows the difference between the pure-tone averages of the left and right control ears of the control group. Three participants in this control group had a pure-tone average difference greater than 10 dB HL. The remaining participants had a pure-tone average difference between the ears of 5 dB HL or less.

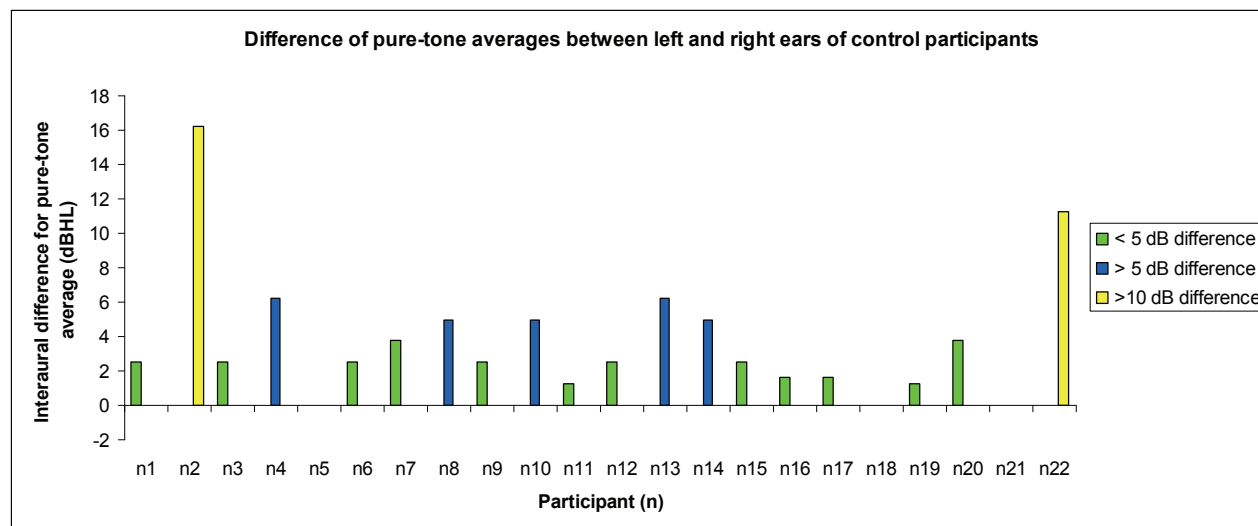


Figure 2.1. This graph shows the pure-tone average (0.5, 1, 2, and 3 kHz) difference between the left and right control ears.

20 adult participants with confirmed definite unilateral Ménière's disease as set out by the American Academy of Otolaryngology-Head and Neck Surgery criteria (Committee on Hearing and Equilibrium Guidelines for the Diagnosis of Ménière's disease, 1995) were approached to participate in the study by Otolaryngologist Prof Jeremy Hornibrook (MBChB, FRACS) from the Christchurch Hospital Ear Nose and Throat Outpatients clinic, Christchurch, New Zealand. From the initial pool of 20 confirmed Ménière's disease patients at Christchurch Hospital, 19 volunteered to participate in the study. Pure-tone audiometry and tympanometry according to the exclusion criteria above eliminated one participant from the study. A total of 18 participants with confirmed Ménière's disease from the wider Canterbury region progressed further in the study. Pure-tone audiometry was used to stage the progression of Ménière's disease in the experimental group. The age of participants in this group ranged from 52 to 77 with a mean age of 60 ± 8 years. The mean pure tone average (0.5, 1, 2 kHz) was 26.2 dB HL for the unaffected ear and 43.3 dB HL for the affected ear which is represented in Figure 2.2. Statistical analysis revealed a significant difference ($p = 0.016$) between the affected and non-affected ears in this group. The ratio of males to females was 3.5:1. Owing to the small number of participants in this group we divided them into an early Ménière group (stages 1 and 2) and

into a late Ménière group (stage 3 and 4). The number of participants in the early group was six and the number of participants in the late groups was twelve. For the rest of the study each participant in this patient group will be labeled from p1 to p18 for individual identification.

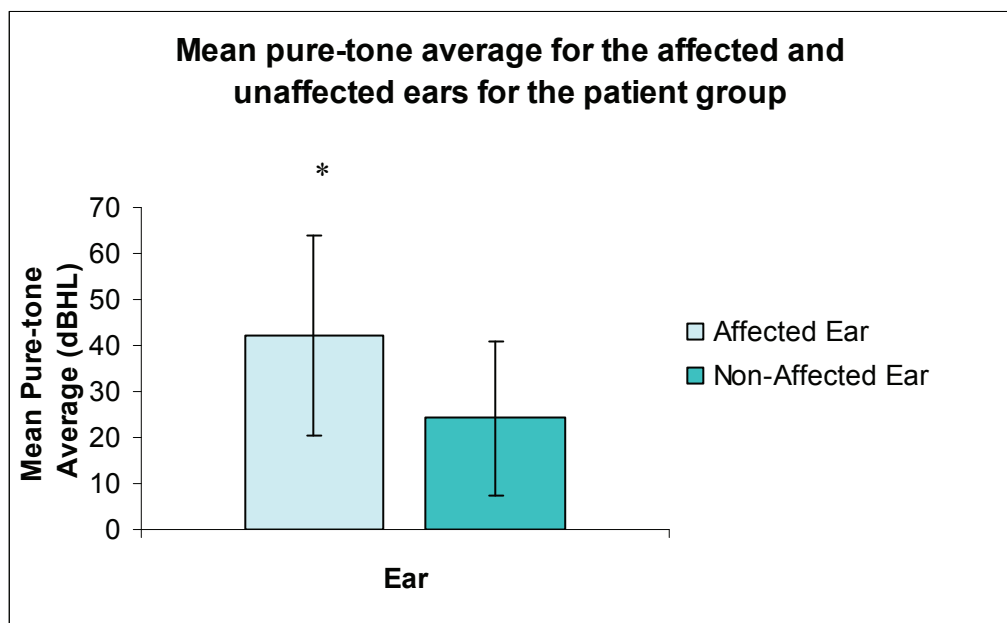


Figure 2.2. This graph shows the mean pure-tone average (0.5, 1, 2 and 3 kHz) for the affected and non-affected ears of the patient group. The astrisk denotes a significant difference between the two groups and the error bars represent the standard deviation of the data.

2.1.1. Electrocochleography (ECochG)

ECochG was performed at Christchurch Public Hospital by Prof Jeremy Hornibrook using the electrodiagnostic system within the ENT department (Amplaid MK 15, Milan, Italy). Electrode configuration consisted of a ground electrode positioned on the forehead and the reference electrode on the earlobe of the test ear. The active electrode, a sterilised transtympanic needle electrode, was punctured through the tympanic membrane and rested against the promontory. Prior to insertion of the transtympanic needle electrode the tympanic membrane was anaesthetised with a drop of phenol. The needle was secured in place by elastic bands attached to a ring positioned over the ear under investigation. During testing the patient was instructed to lie in a supine position to reduce muscle noise during recording. Both air conduction click and tone burst stimuli were applied to elicit an ECochG response via a supra-aural headphone positioned on the ring over the test ear.

Click stimuli (100 μ s) were presented at an intensity of 90 dB HL and a rate of 10 Hz with alternating polarity. The signal was then filtered through a low-pass filter of 2.5 kHz at a 12 dB

per octave slope and a high-pass filter of 0.5 Hz at a 6 dB per octave slope. The analysis time for each response was set to 10 ms and 256 repeats were taken.

In addition, responses from tone burst stimuli were recorded for 500 Hz, 1 kHz, 2 kHz and 4 kHz. Stimulus intensities were 90 dB HL for frequencies 500 Hz to 2 kHz, and 100 dB HL for the 4 kHz response. The rise and fall time was 1 ms with a 14 ms plateau. Analysis time was 30 ms and 1024 repeats were recorded for each response. The band-pass filter was 0.5 Hz – 3 kHz at 6 dB per octave and 12 dB per octave respectively.

ECochG results for participants in the patient group are presented in Table 2.1 below. Comparison of the patient group tone burst ECochG results and the normative data presented in Table 1.6 in Chapter 1 it is clear that all SPs are abnormally large, confirming of endolymphatic hydrops. Furthermore, all click SP/AP ratios are greater than 33% which also provides evidence for endolymphatic hydrops. Participants in the patient group were further assessed using the criteria set out by the AAOHNS and the Gibson ten-point scores. Results from these measures propose that all participants in the control group have definite Ménière's disease as denoted by a 'D' in the AAOHNS column. In addition, the Gibson score for each participant ranges from 7 to 10 with the larger number representing that Ménière's disease is more likely. The AAOHNS criteria and the ten-point scoring system by Gibson (1990) are discussed in Chapter 1.

In conjunction with confirmed definite Ménière's in the affected ears of participants in this patient group a minority also showed the presence of asymptomatic hydrops in the other ear after analysis with ECochG.

Table 2.1. Electrocochleography tone burst (0.5 – 4 kHz) and click stimuli results for the patient group. An SP/AP ratio greater than 33% is considered abnormal for the click stimulus (- = not recorded). All participants tested with the click stimulus had a ratio of 50% or greater. A abnormal SP amplitude is greater than the norms presented in Table 1.6 in Chapter 1 for the tone burst stimuli. The individual Gibson score and diagnosis according to AAOHNS criteria (D = definite) are also included.

Patient	Affected Ear	AAOHNS	Gibson Score	EcochG Results	
				SP/AP click stimulus (> 33% = abnormal SP/AP ratio)	Positive result for tone burst Stimuli (0.5 – 4 kHz)
P1	Left	D	10	73%	1, 2, & 4
P2	Left	D	9	50%	1, 2, & 4
P3	Right	D	9	-	1, & 2
P4	Left	D	10	51%	1
P5	Left	D	10	55.9%	0.5, 1, & 2
P6	Right	D	10	-	0.5, 1, 2, & 4
P7	Right	D	7	-	1, & 2
P8	Left	D	8	-	1, 2
P9	Left	D	10	61%	0.5, & 1
P10	Right	D	7	-	0.5, 1, & 2
P11	Left	D	10	80%	0, 5, 1, & 2
P12	Right	D	10	-	0.5, 1, & 2
P13	Right	D	10	-	1
P14	Right	D	8	53 %	0.5, 1, & 2
P15	Right	D	10	-	0.5, 1, & 2
P16	Left	D	8	56%	2, & 4
P17	Right	D	10	-	0.5, 1, & 4
P18	Right	D	10	-	0.5, 1, & 2

2.2. Instrumentation

2.2.1. Vestibular Evoked Myogenic Software

Custom-written evoked potential averaging software (UC VEMP, shown in Figure 2.3), was developed by Dr Greg O’Beirne using National Instruments LabVIEW 8.20 (National Instruments, TX, USA). The software was used to evoke and record VEMP waveforms, and enable the cervical and ocular VEMP thresholds to be determined. The program controlled the

stimulus characteristics and presentation levels, amplifier and filter settings, and the number of sweeps recorded. The software was run on a Hewlett Packard Compaq nx6120 laptop.

Parameters of the acoustic stimuli were set using the UC VEMP software, and stimuli were delivered via the laptop soundcard to the circumaural headphones as shown on Figure 2.4.

Advantages of the UC VEMP software included;

- the ability to present and record up to eight different intensities,
- self-monitoring of EMG by the patient via an LED light
- the capability to record up to four channels at once
- quick succession of differing intensities during recording

The ability of the software to record multiple channels and intensities at the same time meant that each of the recordings occurred with a similar level of EMG activity. This is significant as it is well documented that the size of the VEMP response is directly associated with the size of the EMG level during testing (Zhou & Cox, 2004; Akin, Murnane, Panus, Caruthers, Wilkinson, & Proffitt, 2004). Self-monitoring of EMG by the way of an LED informed the participant which position was most effective to keep the light glowing, thereby reducing the likelihood of inactivity and over-excision.



Figure 2.3. Screenshot of UC VEMP software showing the waveform acquisition screen. The traces show VEMP waveforms recorded from the right SCM using 500 Hz tone bursts at sound levels of (from top left) 114 dB SPL, 109 dB SPL, 104 dB SPL, and 99 dB SPL. Solid and dashed lines indicate responses evoked by stimuli of different polarity.

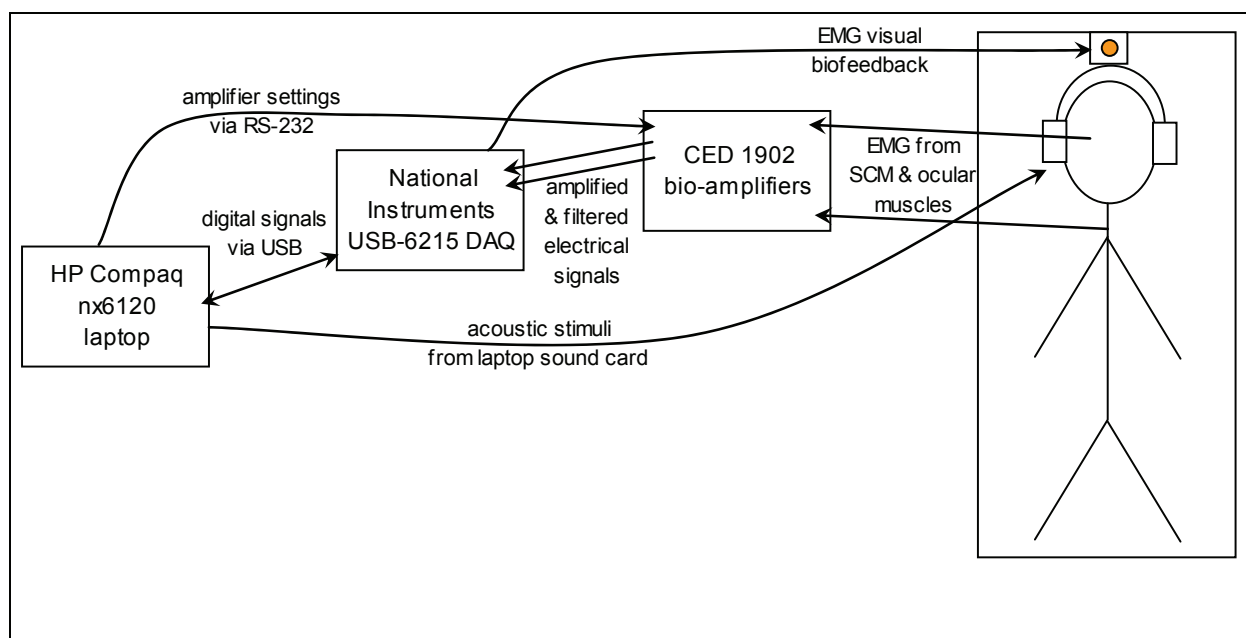


Figure 2.4. Schematic diagram of the equipment used to record VEMPs in the Electrophysiology Lab of the Department of Communication Disorders, University of Canterbury.

A separate programme (UC Evoked Potential Analysis, shown in Figure 2.5) was also developed to speed up the analysis of the ocular and cervical VEMP waveforms (O’Beirne, 2008). This programme allowed the investigator to annotate the important peaks of the VEMP responses and record their latencies and amplitudes. The waveforms produced by each phase of the alternating stimuli could be analysed individually, as well as the sum of those waveforms at each sound level.

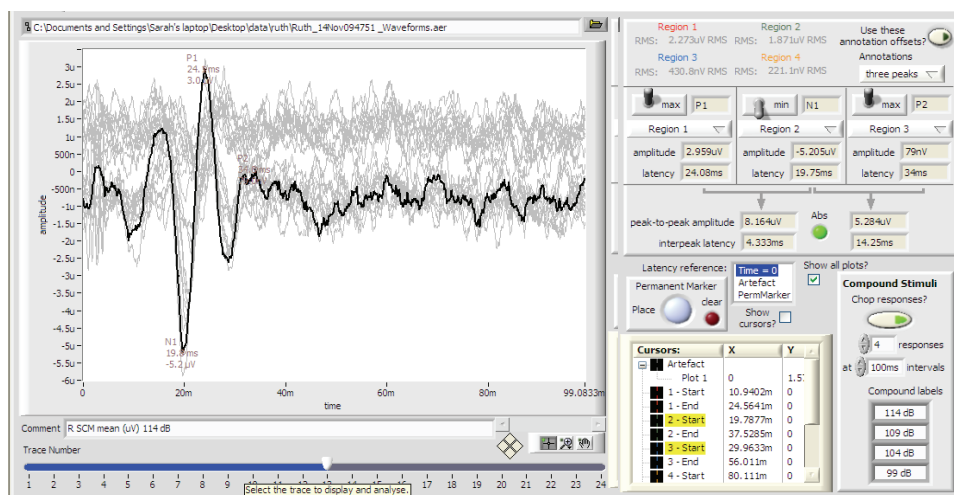


Figure 2.5. Screenshot of UC evoked potential analysis software showing the ocular VEMP waveform. This software enables the researcher to evaluate the peak amplitude and latencies of any evoked potential. All mean, positive and negative waveforms at each intensity can be analysed almost simultaneously.

2.3. Calibration

Calibration of the sound output from the laptop via the circumaural headphones was carried out using a Head and Torso Simulator Type 4128-C (Brüel & Kjær, Nærum, Denmark) in the Department of Mechanical Engineering at the University of Canterbury.

2.4. Procedure

2.4.1. Tympanometry

Tympanometry was performed to ensure participants had normal middle-ear impedance, as any conductive hearing loss would reduce the stimulus level that reached the vestibular system. Normal middle-ear function was defined as a Type A tympanograms with normal admittance, (0.3 - 1.4 mmho), a pressure peak within ± 100 daPa, and an ear canal volume of 0.6 to 1.5 cm³ (ASHA, 1990). All participants who continued on with this study had admittance, ear canal volume and pressure values within normal limits at the time of testing.

2.4.2. Pure-tone Audiometry

Full diagnostic pure tone audiometry took place in a sound treated booth at the University of Canterbury, Communication Disorders Department Audiology Clinic using a GSI clinical audiometer and TDH-39 headphones. The modified Hughson-Westlake procedure determined the air conduction audiometric thresholds for 250, 500, 1000, 2000, 4000, and 8000 Hz for each subject in each ear (Carhart & Jerger, 1959). For frequencies where the air conduction threshold was greater than 20 dB HL, bone conduction pure tone audiometry was performed to determine the bone conduction threshold for that frequency.

2.4.3. Cervical Vestibular Evoked Myogenic Potential Testing

Cervical VEMP testing was performed in the Electrophysiological Lab of the Department of Communication Disorders at the University of Canterbury. The custom-written evoked potential software described above was used to obtain the ocular and cervical VEMP waveforms. The EMG signal was recorded differentially from silver/silver chloride surface electrodes (Ag/AgCl Blue Sensor, Ambu A/S, Denmark). Active electrodes were placed over the middle part of each SCM body, as this is reported to be the optimal electrode positioning for recording reliable and repeatable VEMPs (Sheykholeslami, Murofushi, & Kaga, 2001). The indifferent electrodes were placed on the upper sternum whilst the ground electrode was placed on the forehead, as recommended by Sheykholeslami & Kaga (2002), Ochi, & Ohashi (2003), and Patko, Vidal, Vibert, Huy, & de Waele (2003). These electrodes measured the change in electrical activity in response to the acoustic stimulus and the CED 1902-11/4 electrode adapter fed this information back to the software via two CED amplifiers as indicated on Figure 2.4.

The impedance of the electrodes was reduced by the removal of dead skin cells with alcohol wipes around the area of interest. The EMG signal obtained by the differential recording was band pass filtered between 10 - 2000 Hz and amplified (Gain 3000x) using a CED 1902 bio-amplifier (Cambridge Electronic Design, Cambridge, UK), and digitized by a NI USB-6215 DAQ card (National Instruments, TX, USA).

Circumaural headphones delivered the acoustic stimulus produced by the UC VEMP software from the soundcard to the participant. The parameters of the stimuli were selected after consideration of those used by other researchers, as detailed in Table 2.2. The acoustic

stimulus, an alternating 500 Hz tone burst, was presented initially at 114 dB SPL monaurally to each ear. The rise and fall time of the tone burst was set to 1 ms with a 2 ms plateau. While some previous researchers have used an inter-stimulus interval of 200 ms (i.e. a repetition rate of 5 Hz), our preliminary testing with a 10 Hz repetition rate indicated little change in response amplitude, but a considerable reduction in test time. Responses from 256 repetitions were averaged to produce each waveform.

During recording, each participant was required turn towards the ear contralateral to that receiving the stimulus and to lift their head from a supine position to maintain tonic muscle activity in the ipsilateral SCM. Activation of the SCM is a key determinant of the VEMP response as the amplitude of the VEMP response is dependent on SCM tonic activity (Akin et al. 2004). Throughout the recording, the principle investigator monitored the level of EMG activity to ensure that sufficient contraction occurred at the ipsilateral SCM. Furthermore, a red LED light attached to the wall in the line of sight of the participant indicated the level of tonic EMG activity, thereby enabling self monitoring of SCM contraction level. For example, when the EMG activity fell below 30 μ V the LED light turned off, indicating to the participant that they were required to tense their neck further. Furthermore, all EMG activity was recorded by the UC VEMP software for later analysis. No maximum EMG level was enforced.

Responses were recorded at four stimulus levels simultaneously using an interleaved protocol, enabling variations in response amplitude due to stimulus level to be separated from any effects of EMG level. The first four levels were 114 dB SPL, 109 dB SPL, 104 dB SPL and 99 dB SPL. If a response could be visually identified by the primary investigator at each of those levels, then the intensity was further reduced until threshold was reached. Threshold was defined as the lowest stimulus level at which a repeatable response was seen by the principal investigator. Every response was saved for further analysis using the UC evoked potential analysis software.

Parameter	Pakto et al. (2003)	Young & Kuo (2004)	Rauch et al. (2004b)	Sheykholeslami & Kaga (2002)	Wang & Young (2004)	Young et al. (2002)
Reference Electrode	upper sternum	upper sternum	tendon above clavicle	Upper sternum	upper sternum	upper sternum
Active Electrode	upper SCM	upper SCM	upper 3 rd SCM	Middle SCM	upper SCM	upper SCM
Earth Electrode	Forehead	-	Forehead	Forehead	forehead	-
Band Pass Filter	0.01 – 1.6 kHz	0.03 – 3 kHz	0.01 – 2 kHz	0.02 – 2 kHz	0.03 – 3 kHz	0.03 – 3 kHz
Stimulus Rate	5 Hz	5 Hz	-	-	5 Hz	5 Hz
Intensity	100 dBHL	95 dBHL	90 dBHL	70 dBnHL	100-95 dBHL	95 dBHL
Stimulus Duration	1–2-1 ms	1-2-1 ms	two cycles	1-2-1 ms	1-2-1 ms	2-2-2 ms
Patient Position	Supine	Supine	Upright	Supine	supine	supine
Analysis Time	100 ms	60 ms	30 ms	100 ms	60 ms	50 ms
Type of Stimulus	0.5 kHz tone burst	0.5 kHz tone burst	.25 – 4 kHz tone burst	0.5 kHz tone burst	0.5 kHz tone burst	0.5 kHz tone burst
Averages	512	200	100 +	128	200	200
Sampling rate	30 kHz	-	-	-	-	-

Table 2.2. Parameters for the cervical VEMP as described by the above authors, indicating the sampling rate, subject position, stimulus applied, and number of averages.

2.4.4. Ocular Vestibular Evoked Myogenic Potential Testing

The test procedure for the ocular VEMP was largely similar to that of the cervical VEMP with the following exceptions:

- The electrode configuration involved the placement of the active electrode directly beneath the eye over the inferior oblique muscle of the eye as found optimal by Rosengren et al. (2005) and Chihara et al. (2007). The reference electrode was positioned 1-2 cm below the active over the cheek. The earth electrode was placed on the forehead for the differential recording.
- During recording participants were required to maintain eye gaze in the superomedial direction throughout recording (Chihara et al., 2007).
- The threshold of the red LED light was set between 4-6 μV .
- The averaged waveform from 512 responses was replicated for each attenuated intensity level in each ear.
- The vertical gaze angle was not measured.

The stimulus characteristics from the literature are presented in Table 2.3.

	Todd et al.(2008)	Todd et al. (2007)	Chihara et al. (2007)	Rosengren et al. (2005)
Reference Electrode	2-3 cm below active	2-3 cm below active	1-2 cm below active	earlobe
Active Electrode	directly below eye	directly below eye	Directly below eye	-
Earth Electrode	Sternum	sternum		sternum
Band Pass Filter	0.05 -1 kHz	0.05 -1 kHz	0.05 - 500 Hz	0.05 - 300 Hz
Sample Rate	5 kHz	10 kHz	-	10 kHz
Artifact Rejection	Yes	Yes	-	-
Patient Position	Upright	supine	Sitting	supine
Optimal Gaze	Vertical	-	Superomedial	superomedial
Repetitions	500	1000	100	500
Stimulus Rate	8 Hz	5 Hz	5 Hz	5 Hz
Stimulus Type	head accelerations	500 Hz tone burst (AC and BC)	500 Hz tone bursts	500 Hz bone conduction
Duration of Stimulus	4 ms	2 ms	1 ms – 2 ms – 1 ms	1 ms – 6 ms – 1 ms
Polarity	-	alternating	-	-
Output/Intensity	-	141.4 dBSPL (AC)- 135 dB (BC)	135 dBSPL (121.5 dBHL)	-
Analysis Time	70 ms	60 ms	50 ms	60 ms

Table 2.3. Parameters for the ocular vestibular evoked myogenic potential as described by: Rosengren et al. (2005); Chihara et al. (2007); Todd et al. (2007); and Todd et al. (2008).

2.5. Measures

The threshold, amplitude, interaural amplitude difference ratio and latency of both the ocular and cervical VEMP responses were analysed and compared to investigate which VEMP testing procedure was more reliable in staging and detecting participants affected by Ménière's disease. Both the affected and unaffected ears of the experimental group, and the left and right ears of the control group were analysed. In addition to analysis of the waveforms evoked by alternating stimuli, analysis was also carried out on waveforms evoked by a single polarity (i.e. an initial condensation or initial rarefaction). Consequently, the number of averages for the condensation and rarefaction waveforms were half of that of the alternating waveforms.

2.5.1. Threshold

The lowest level in decibels that resulted in a response was determined as the threshold. The threshold was recorded in both the asymptomatic, symptomatic and control ears for both the ipsilateral and contralateral ocular and cervical VEMPs. The threshold was determined by the principal investigator by visual inspection of the waveforms and was analysed to determine its use as a method for diagnosing Ménière's disease.

2.5.2. Amplitude

The first negative (n1) and two positive (p1 and p2) peaks of the cervical VEMP waveform were identified and labelled by the UC Evoked Potential Analysis programme. Furthermore, the peak-to-peak N1P2 amplitude and P1N1 amplitudes were also measured. With regard to the ocular VEMP the first three positive (p1, p2 and p3) and negative peaks (n1, n2 and n3) and the N3P3 amplitude, P2N3 amplitude, P1N2 amplitude and N1P1 amplitude peak-to-peak measures were evaluated. Each individual peak was measured from the zero baseline. Given the high-pass filter in the recording system, this baseline corresponded to the long-term RMS average of the recorded EMG. The amplitudes for each ipsilateral and contralateral presentation in both the left and right ears were recorded for both groups. In conjunction, the individual condensation and rarefaction waveforms and alternating waveforms for both the ocular and cervical VEMPs were measured.

2.5.3. Latency

The time at which these waveform peaks occurred (the peak latency) was recorded for each of the responses. Analysis of P1P2 peak-to-peak latency for the cervical VEMP was also included.

2.5.4. Interaural Amplitude Difference Ratio

. The interaural amplitude difference ratio (IAD) measured the amplitude difference between the affected and non-affected ears in the experimental group and between the left and right ears in the control group.

- $(\text{right control data} - \text{left control data}) / (\text{right control data} + \text{left control data})$
- $(\text{asymptomatic Ménière data} - \text{symptomatic Ménière data}) / (\text{asymptomatic Ménière data} + \text{symptomatic Ménière data})$

The peak-to-peak amplitude measures for the cervical VEMP included the N1P2 and P1N1 measures. In addition, the N1P1, P2N3, N3P3 and P1N2 peak-to-peak amplitude measures of the ocular VEMP were applied to both the ipsilateral and contralateral response data. Furthermore, the alternating condensation and rarefaction waveforms were evaluated in every scenario.

2.5.5. Electromyographic Activity

The electromyographic (EMG) activity of both the inferior oblique and sternocleidomastoid muscles were recorded throughout testing. The average EMG for each channel for the period of the entire recording window was recorded. This was done for both ears of the patient and control groups and was evaluated and compared.

2.5.6. Questionnaire

A simple questionnaire was given to all control and Ménière participants in this study by email or phone. The aim of the questionnaire was to determine which VEMP task was easier to perform. The questionnaire is attached in the Appendix.

2.6. Statistical Analysis of Results

Statistical analysis using the paired t-test, standard t-test and the one-way ANOVA test was applied. The Kruskal-Wallis one-way ANOVA test was chosen owing to the unequal number of participants in each patient group to determine a difference between the control and patient groups for both the ocular and cervical VEMP tests. To ascertain this amplitude, latency, IAD ratio and threshold of the VEMP responses were evaluated. A statistically significant result was accepted when the p value was less than 0.05. After reaching statistical significance with the Kruskal-Wallis one-way ANOVA test a multiple comparison pair-wise procedure took place using Dunn's method for post-hoc multiple comparisons to determine the statistical significance between each group. SigmaStat Software 3.5 (Systat Software Inc, 2006) was used for all statistical evaluations.

CHAPTER THREE

RESULTS

3. Results

This chapter reviews the results and statistical analyses from the 22 control and 18 Ménière participants in this study. The interaural amplitude difference ratio, EMG level, amplitude, latency and threshold of the cervical and ocular responses were analysed. In addition, a questionnaire was included to determine the relative difficulty of the two VEMP tasks.

We did not anticipate that there would be any differences in the VEMP evoked for the left and right ears of control participants. However, statistical analyses of the results collected from the left and right control ears revealed significant between the ears for:

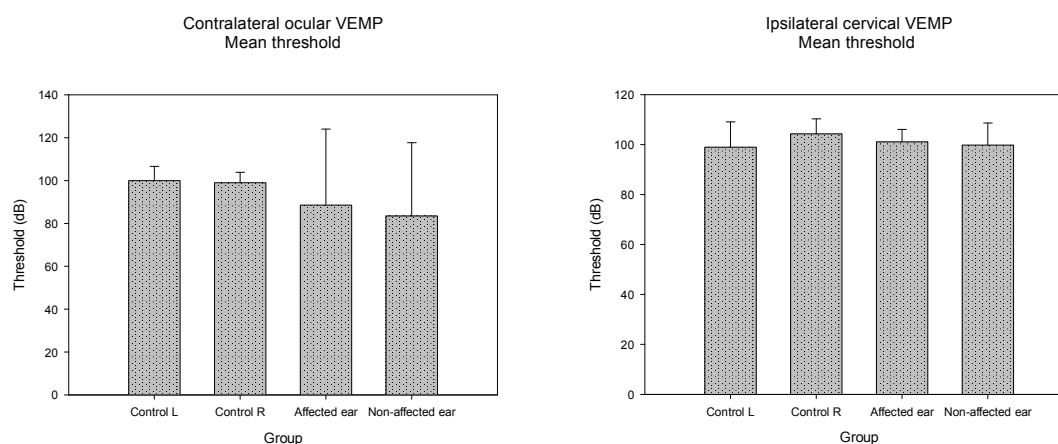
- i) a number of amplitude and latency measures for contralateral ocular VEMP (Table 6.3.1 in Appendix 1).
- ii) P2 latency measure for the ipsilateral cervical VEMP (Table 6.3.2 in Appendix 1);
- iii) the threshold measures for the ipsilateral cervical VEMP (Table 6.3.3 in Appendix 1);

The differences between the control ears may be attributable to differing EMG levels during testing (refer to section 3.6). Due to these differences, the left and right control ears were treated as separate groups, termed control L and control R respectively. Due to the small sample size in each stage of Ménière's disease in this study, the first and second stages were combined to form the first Ménière group (M1); with the remaining third and fourth stages grouped to form the second Ménière group (M2). All analyses were performed to test the null hypothesis of the study, that there is no significant difference in the sensitivity of the cervical and ocular VEMPs in detecting endolymphatic hydrops as a result of Ménière's disease.

3.1. Threshold

To establish whether the thresholds of the ocular and cervical VEMP could be used as a diagnostic tool in the diagnosis of Ménière's disease, statistical analysis was performed on the two control groups, L and R, and the Ménière groups, M1 and M2. This analysis was aimed at providing a comparison between all groups. The Kruskal-Wallis one-way ANOVA on ranks test was applied. The lowest intensity at which a repeatable VEMP waveform was produced

was established as the threshold. The threshold was measured for both ipsilateral and contralateral presentation for the ocular and cervical VEMP responses. In addition, the two stimulus polarities and the averaged waveform were individually analysed and the affected and non-affected ears were evaluated.



Figures 3.1 and 3.2. Show the mean thresholds for the control and Ménière groups of the cervical VEMP (Figure 3.1) and the ocular VEMP (Figure 3.2).

The paired t-test was performed on the threshold data for the left and right ears for the control group. Results revealed a statistically significant difference for the mean ($p = 0.009$) and condensation (positive) ($p = 0.012$) waveforms for the ipsilateral cervical VEMP, as shown in Table 6.1.2 (see Appendix 1). Conversely, statistical analysis of the contralateral ocular VEMP indicated no significant differences between the two sets of control data as shown in Table 6.2.3 (see Appendix 1). However, for consistency, the left and right control data (control L and R) were treated separately in the statistical analyses.

The Kruskal-Wallis ANOVA on ranks test was applied to the contralateral ocular VEMP threshold data when sound was presented to the non-affected and affected ears (Figure 3.3).

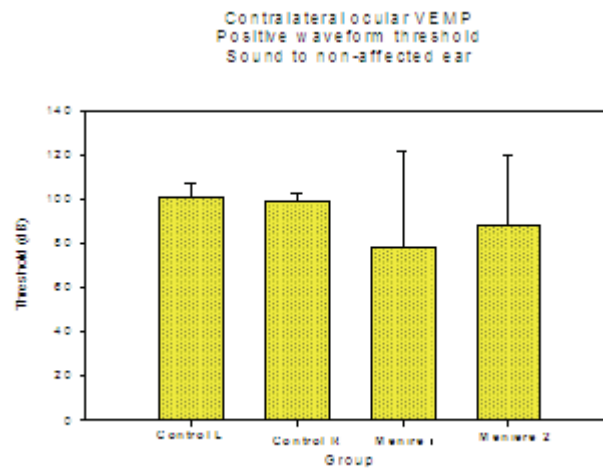


Figure 3.3. Threshold of the condensation (positive) stimuli for the control data (L and R) and Mènière groups (1 and 2) when sound was presented to the non-affected ear. The response is from the ocular VEMP with contralateral presentation.

Analysis of the ocular and cervical VEMP thresholds when sound was presented to the affected ear revealed no significant differences between the control L or control R and M1 or M2 groups. This was the case for each of the three individual waveforms, as depicted in Tables 6.1.2 and Table 6.2.3 (see Appendix 1).

Further analysis of the data with the Kruskal-Wallis ANOVA on ranks test was performed on the non-affected ears of the Mènière group for the cervical VEMP. This resulted in a statistically significant ($p = 0.039$) finding for the condensation (positive) waveform. The post-hoc multiple pair-wise comparisons using the Dunn's method did not reveal any differences between any of the groups however, as shown in Figure 3.3. The mean threshold of both Mènière groups for this condensation (positive) stimulus (85.1 ± 33.1 dB SPL) was reduced compared to the mean of the control groups (99.0 ± 5.3 dB SPL). The remaining results for both the ipsilateral cervical and contralateral ocular VEMPs for all three stimuli, the alternating, condensation and rarefaction stimuli, produced no significant differences, as illustrated in Table 6.1.2 and Table 6.2.3 (see Appendix 1).

Overall, the threshold measure did not produce any significant results when sound was presented to the affected ear for the cervical and ocular VEMP tests. The only significant result arose for the condensation (positive) waveform when sound was presented to the non-affected ear with the contralateral ocular VEMP response. These results are not consistent

with our hypothesis that the Ménière groups would have a higher intensity threshold compared to the control group.

3.2. Amplitude and Peak-to-peak Amplitude Measures

The peak amplitudes of the cervical and ocular VEMP responses at an intensity of 114 dB SPL were evaluated to determine whether this measure could identify a difference between the control and Ménière groups. The 114 dB SPL data was used as it was the most complete set of data. The peak amplitude was calculated for the first three peaks of the cervical VEMP (Figure 3.5) and first six peaks of the ocular VEMP (Figure 3.4). The amplitudes of these peaks were compared to both the left and right ear control data because the paired t-test revealed significant differences between the ears for a minority of measures in this study (Appendix 1). This comparison was also made for consistency between the tests.

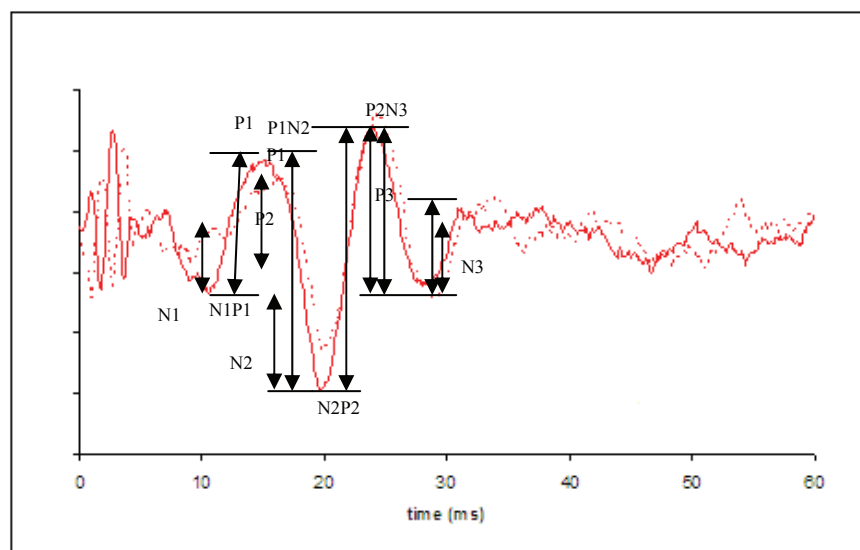


Figure 3.4. Contralateral ocular VEMP response for the condensation and rarefaction waveforms demonstrating the peaks (N1, P1, N2, P2, N3 and P3) and peak-to-peak amplitude (N1P1, P1N2, P2N3 and N3P3) measures investigated.

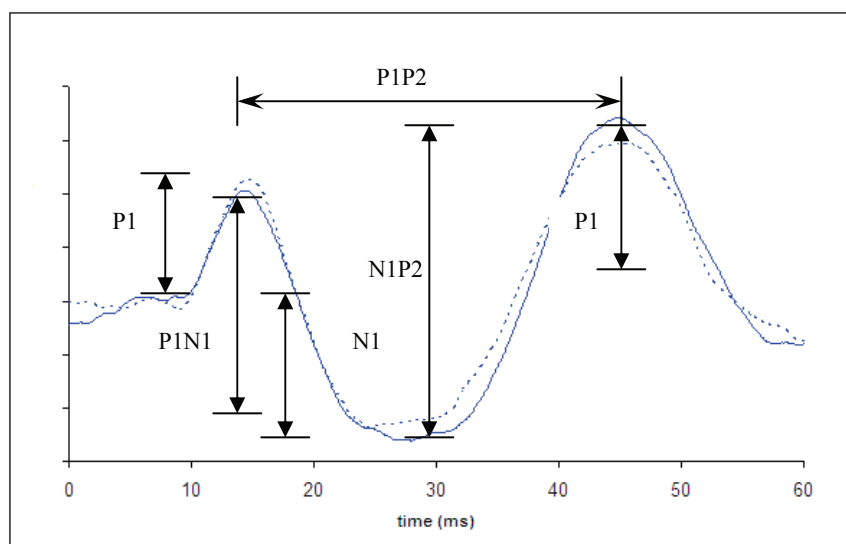


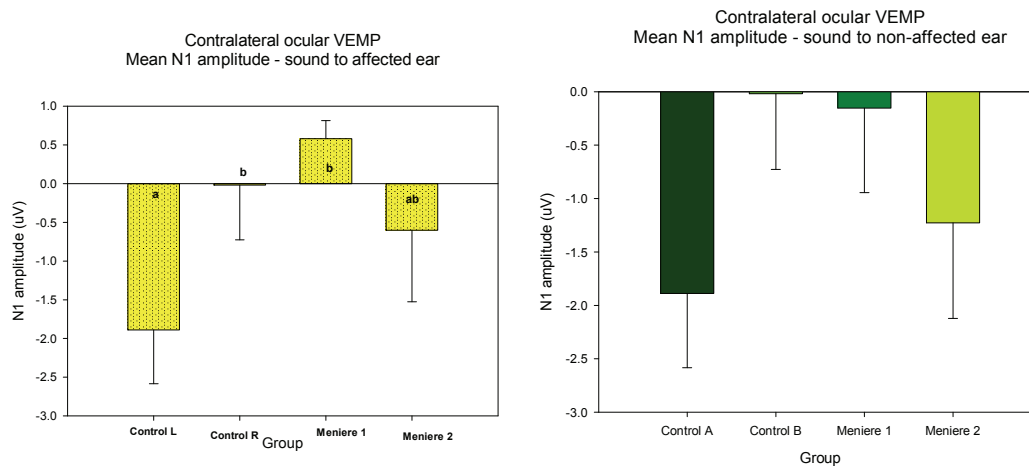
Figure 3.5. Ipsilateral cervical VEMP response for the rarefaction and condensation waveforms demonstrating the peaks (P1, N1 and P2) and peak-to-peak amplitude (P1N1 and N1P2) and peak-to-peak latency (P1P2) measures investigated.

3.2.1. Amplitude and Peak-to-peak Amplitude Measures of the Contralateral Ocular VEMP

To determine whether the peak amplitude of the ocular VEMP could be used as a measure to diagnose Ménière's disease, the amplitude of the first negative (N1) and positive (P1), second negative (N2) and positive (P2), and third negative (N3) and positive (P3) peaks were analysed, as depicted in Figures 3.4 and Figure 3.5. In addition, the N1P1, P1N2, P2N3 and N3P3 inter-amplitude measures were evaluated as additional indicators.

Overall, results of the Kruskal-Wallis ANOVA on ranks revealed a significant reduction ($p = < 0.001$) in the amplitude of the N1, P1, and N2 peaks of the ocular waveform when sound was presented to either the affected and non-affected ears with the alternating polarity stimulus, as shown in Table 6.2.1 (see Appendix 1). A significant difference between the L and R control groups was found for the four measures discussed below.

Dunn's method for post-hoc multiple pair-wise comparisons was performed on the N1 amplitude measure. Results for the affected and non-affected ears are shown in Figures 3.4 and 3.5.

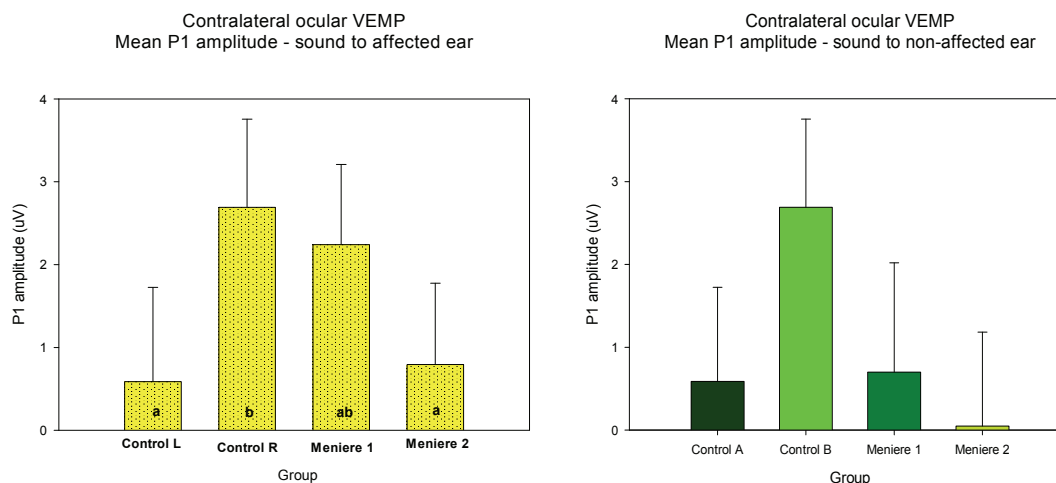


Figures 3.6 and 3.7. Mean N1 amplitude for the control groups L and R and the Ménière groups 1 and 2 when sound was presented to the affected ear (Figure 3.6) and non-affected ear (Figure 3.7) for the contralateral ocular VEMP response. Group means that are significantly different from each other are labelled with different letters.

The mean amplitude of the N1 peak was $0.6 \pm 1.0 \mu\text{V}$ when sound was presented to the affected ear in the first Ménière group. In comparison, the N1 amplitude of control group L was $-1.9 \pm 0.7 \mu\text{V}$. These amplitudes were determined to be significantly significant (Figure 3.6). In contrast there was no significant difference between the second Ménière group and either control group L or R.

When sound was presented to the non-affected ear for the N1 amplitude measure a significant difference with the Kruskal-Wallis ANOVA on ranks test was revealed between the test groups investigated. However, no significant difference was found between the Ménière and control groups when the Dunn's method for multiple comparisons was applied (Figure 3.7).

Dunn's method for post-hoc multiple pair-wise comparisons was performed on the contralateral ocular VEMP for the P1 amplitude measure. Results for the affected ear are displayed in Figure 3.8, and in Figure 3.9 for the non-affected ear.

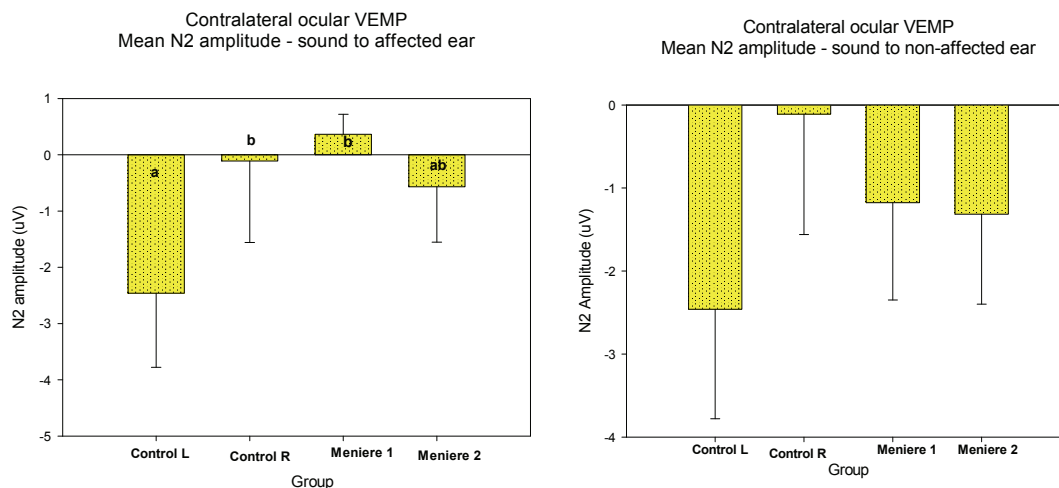


Figures 3.8 and 3.9. Mean P1 amplitude for the control groups L and R and Ménière groups 1 and 2 for the contralateral ocular VEMP when sound was presented to the affected ear (Figure 3.8) and non-affected ear (Figure 3.9). Group means that are significantly different from each other are labelled with different letters.

As seen in Figure 3.8, a significant difference between the second Ménière group and control group R was found when sound was presented to the affected ear. The mean amplitude for the second Ménière group was reduced ($0.8 \pm 1.0 \mu\text{V}$) compared to the control group R ($2.7 \pm 1.1 \mu\text{V}$). No significant difference between the Ménière 1 patient group and the control groups L and R was found.

A significant difference was found between the second Ménière group and control group R for the P1 amplitude measure for the non-affected ear (Figure 3.9). A significant decrease in amplitude between these groups was determined for the alternating stimuli. The amplitude of the second Ménière groups was $0.1 \pm 1.2 \mu\text{V}$.

Post-hoc multiple pair-wise comparisons using Dunn's method was applied to the contralateral ocular VEMP N2 amplitude data. Figures 3.10 and 3.11 display the affected and non-affected ear statistical data, respectively.

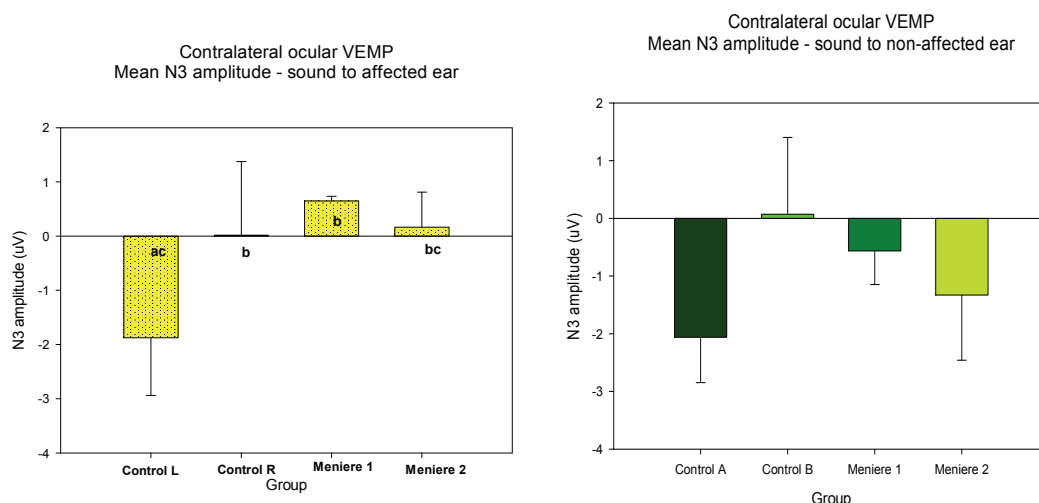


Figures 3.10 and 3.11. Mean N2 amplitude for the contralateral ocular VEMP when sound was presented to the affected (Figure 3.10) and non-affected (Figure 3.11) ears for the control (L and R) and Ménière groups (1 and 2). Group means that are significantly different from each other are labelled with different letters.

A reduction in amplitude of N2 for the first Ménière group compared to control group L is displayed in Figure 3.10 for the affected ear. The mean amplitude of the first patient group was $0.4 \pm 1.0 \mu\text{V}$, compared to the amplitude of control group L which was $-2.7 \pm 1.9 \mu\text{V}$. Analysis with control group R did not reveal any significant differences between the patient groups.

Results from the non-affected ear revealed a significant difference between the experimental groups with the one-way ANOVA method on ranks, shown in Figure 3.11. Post-hoc multiple comparisons using Dunn's method however, failed to determine a significant difference between any of the control and Ménière groups.

Dunn's method for post hoc multiple comparisons was performed on the N3 amplitude measure. Results for the non-affected and affected ear are displayed in Figures 3.12 and 3.13.



Figures 3.12 and 3.13. N3 amplitude for the control (L and R) and Ménière groups (1 and 2) when sound was presented to the contralateral ear for both the affected (Figure 3.12) and non-affected ears (Figure 3.13) for the ocular VEMP response with alternating polarity. Group means that are significantly different from each other are labelled with different letters.

Results for the N3 amplitude measure when sound was presented to the affected ear revealed a significant reduction in amplitude of the N3 response (Figure 3.12). The amplitude of the M1 and M2 Ménière groups was $0.7 \pm 0.6 \mu\text{V}$ and $0.2 \pm 0.7 \mu\text{V}$ respectively. The amplitude of the response in the second Ménière group was smaller compared to the first patient group, but failed to reach statistical significance ($p = 0.376$). Dunn's method for post hoc multiple comparisons determined significant differences between both Ménière groups compared to control group L which had a amplitude of $-2.1 \pm 0.8 \mu\text{V}$. This N3 amplitude measure was the only result which reached significance for both Ménière groups compared using the contralateral ocular VEMP. Comparisons made between the patient groups and control group R failed to reach any significance.

One-way ANOVA on ranks revealed a significant group effect when sound was presented to the non-affected ear for the N3 amplitude measure. However, no significant difference between the control and Ménière groups was determined using the Dunn's method for multiple comparisons (Figure 3.13).

The condensation and rarefaction polarities produced similar results, as shown in Table 6.2.1 (Appendix 1). Due to the similarity of the findings they are not discussed in this chapter

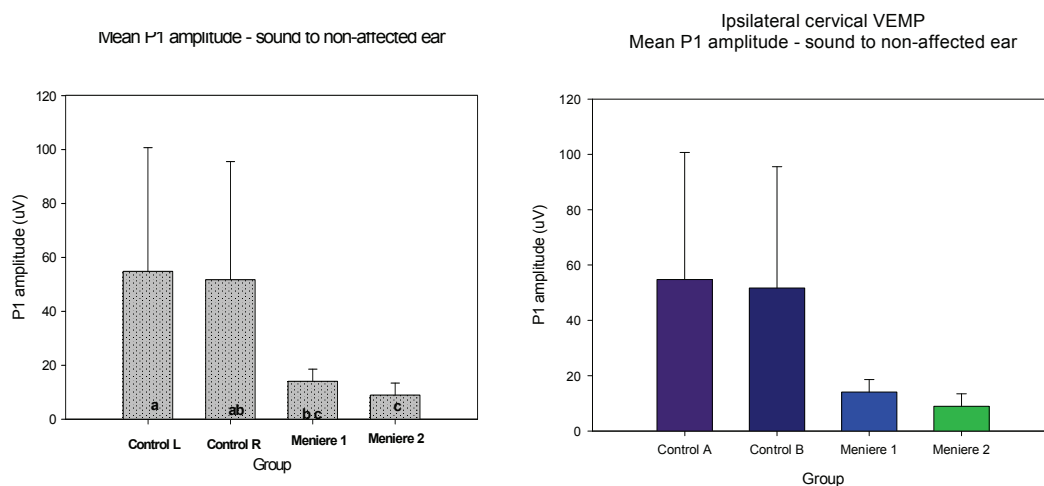
nor are the other statistically significant ($p = \leq 0.05$) results for the contralateral ocular VEMP which are illustrated in Table 6.2.1.

In summary, a significant reduction in amplitude for the N1, P1, N2 and N3 amplitude measures of the Ménière groups was found compared to the control groups. In particular the N2 amplitude measure determined a significant group effect for both Ménière groups compared to control group A. Results from the ocular VEMP produced significant differences with the one-way ANOVA on ranks method when sound was presented to the non-affected ear for the above measures however, Dunn's method failed to determine any significant differences between the control and Ménière groups. For these reasons, the presentation of acoustic stimuli to the affected ear provides stronger evidence of hydrops.

3.2.2. Amplitude and Peak-to-peak Amplitude Measures of the Cervical VEMP

To determine if the cervical VEMP could be applied as a diagnostic test for Ménière's disease the amplitude of the P1, N1, P1N1 and N1P2 peaks and peak-to-peak amplitudes were analysed. The Kruskal-Wallis one-way ANOVA on ranks method performed on the P1 and P1N1 amplitude measures for the alternating and condensation stimuli reached statistical significance ($p = < 0.001$). Furthermore, the N1, N1P2 also reached statistical significance ($p = 0.05$). Both the left and right ear control data was included as part of the analysis as initial investigation revealed significant differences between the ears for a proportion of the amplitude measures.

Dunn's method for post-hoc multiple pair-wise comparisons was applied to the P1 amplitude measure of the ipsilateral cervical VEMP. The results for the affected ear (Figure 3.14) and non-affected ear (Figure 3.15) are displayed below.



Figures 3.14 and 3.15. Mean P1 amplitude for the ipsilateral cervical VEMP when sound was presented to the affected ear (Figure 3.14) and non-affected ear (Figure 3.14) for the control (L and R) and Ménière groups (1 and 2). Group means that are significantly different from each other are labelled with different letters.

Statistical analysis determined a significant reduction in amplitude between control group L and both Ménière groups 1 and 2 when sound was presented to the affected ear, as seen in Figure 3.18. The mean amplitudes for these groups are as follows; control group L ($54.9 \pm 45.9 \mu\text{V}$); early Ménière group ($14.1 \pm 4.2 \mu\text{V}$); late Ménière group ($9.0 \pm 4.5 \mu\text{V}$). No significant difference between the two Ménière groups was found. A significant reduction in amplitude was revealed between the second Ménière group and control group R ($51.8 \pm 43.9 \mu\text{V}$).

Dunn's method for post-hoc multiple comparisons revealed a statistically significant reduction in P1 amplitude between control groups L and R and Ménière group 2 when sound was presented to the non-affected ear. The amplitude of the control groups was $54.8 \pm 45.9 \mu\text{V}$, $51.7 \pm 43.8 \mu\text{V}$ respectively, and for the Ménière groups was $26.8 \pm 16.7 \mu\text{V}$ and $16.2 \pm 14.5 \mu\text{V}$ respectively, as shown in Figure 3.15.

Post-hoc multiple comparisons using Dunn's method analysed the P1N1 peak-to-peak amplitude of the ipsilateral cervical VEMP. Results from the affected ear are shown in Figure 3.16.

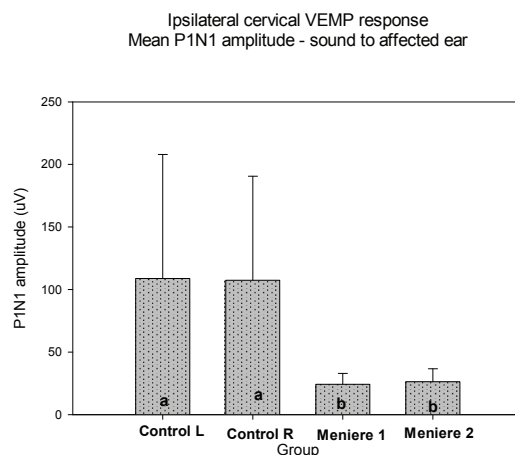


Figure 3.16. Mean P1N1 peak-to-peak amplitude for the ipsilateral cervical VEMP when sound was presented to the affected ear for the control and Ménière groups. Group means that are significantly different from each other are labelled with different letters.

Analysis of the P1N1 peak-to-peak amplitude revealed a significant difference between the late and early Ménière groups with both control groups. This measure was the only amplitude and latency measure that reached significance with both control groups. The mean amplitude of the early and late Ménière groups was $24.3 \pm 8.8 \mu\text{V}$ and $26.3 \pm 10.4 \mu\text{V}$, respectively, compared to the mean amplitudes of control groups L ($108.9 \pm 99.0 \mu\text{V}$) and R ($107.4 \pm 83.1 \mu\text{V}$). This significant reduction in the amplitude of the P1N1 peak-to-peak amplitude measure, is displayed in Figure 3.16.

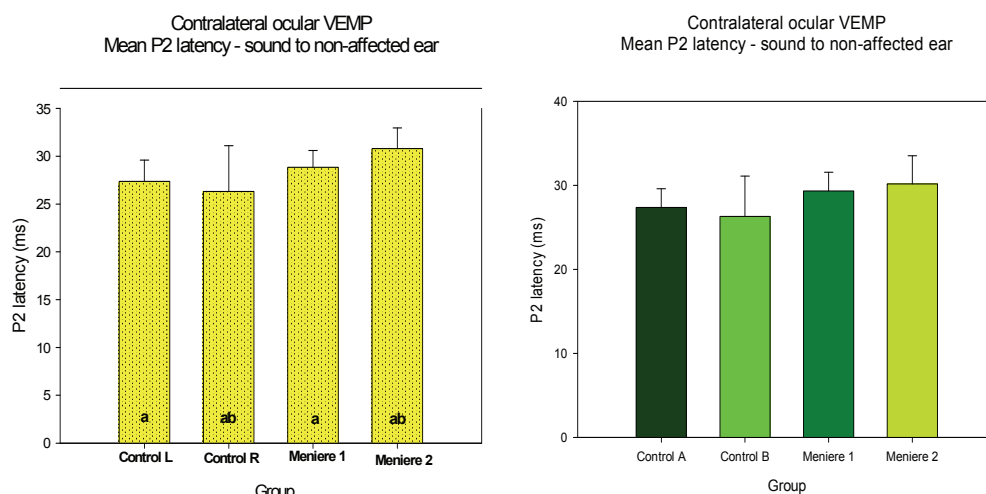
Overall, the waveform evoked with an initial rarefaction (negative) produced results which had less ability to differentiate between the Ménière and control groups, as seen in Table 6.1.1 (Appendix 1). Both the condensation (positive) and alternating waveforms produced results with a higher level of significance for the P1 and P1N1 amplitude measures when sound was presented to the affected ear. A clear reduction in the amplitude of the early and late Ménière groups was established with the one-way ANOVA test, however no significance was determined when Dunn's method for post-hoc multiple comparisons was applied.

3.3. Latency Measures

3.3.1. Latency Measures of the Ocular VEMP

To establish if the latency of the ocular VEMP was different in ears with and without hydrops the N1, P1, N2, P2, N3 and P3 latency measures were investigated. The Kruskal-Wallis one-way ANOVA on ranks test determined significant results ($p \leq 0.05$) for the P2 and N3 latencies. Similar findings were established between each of the three polarities investigated. In contrast to the amplitude measures of the ocular VEMP findings where statistical results had a p-value less than 0.01, the peak latency measures reached significance when the p value was less than 0.05. This suggests that the amplitude measures provide stronger evidence for distinguishing the Ménière groups from the controls than the latency measures.

Dunn's method for post-hoc multiple comparisons was applied to the P2 latency measure for the contralateral ocular VEMP. Results for the non-affected and affected ears are presented in Figures 3.17 and 3.18, respectively.

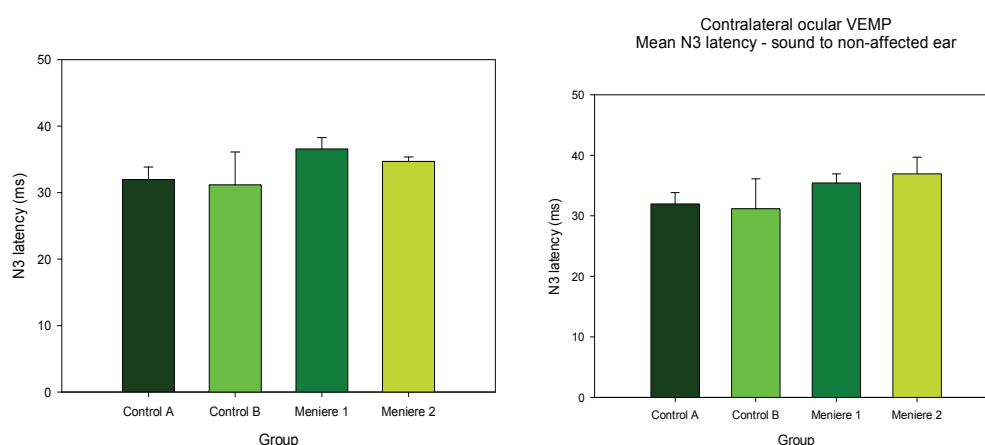


Figures 3.17 and 3.18. Mean P2 latency of the contralateral ocular VEMP when sound was presented to the affected ear (Figure 3.17) and non-affected ear (Figure 3.18) for the control and Ménière groups. Group means that are significantly different from each other are labelled with different letters.

The stimulus with alternating polarity produced a significant difference for the P2 latency measure between the second Ménière group and control group R ($p = 0.029$). The mean latencies were 26.8 ± 4.9 ms and 30.8 ± 2.2 ms for control group R and Ménière group M2

respectively. This indicates an increase in latency in the later stages of Ménière's disease when sound was presented to the affected ear, as seen in Figure 3.17. The non-affected ear data for this measure did not reach significance, as shown in Figure 3.18.

Application of the Kruskal-Wallis one-way ANOVA on ranks test on the N3 latency data for the contralateral ocular VEMP was performed. Figures 3.19 and 3.20 display the statistical results for the affected and non-affected ears respectively.



Figures 3.19 and 3.20. Mean N3 latency of the contralateral ocular VEMP measure when sound was presented to the affected ear (Figure 3.19) and non-affected ear (Figure 3.18) for both the control (L and R) and Ménière groups (1 and 2). Group means that are significantly different from each other are labelled with different letters.

One-way ANOVA on ranks revealed a statistically significant increase in latency ($p = 0.015$) when sound was presented to the affected ear for the N3 peak. However, the post-hoc multiple pair-wise comparisons using Dunn's method revealed no significant differences between any of the groups analysed as depicted in Figure 3.19. These findings were similar for the non-affected ear results as shown in Figure 3.20.

Overall, the latency measures for the ocular VEMP response produced statistically significant results for the P2 and N3 peaks with the one-way ANOVA on ranks test. However, application of the Dunn's method for post-hoc multiple pair-wise comparisons failed to determine a difference between each of the groups for the N3 measure. In contrast, the P2 latency measure determined a significant increase in latency between the later stages of Ménière's disease and control group R with this test.

3.3.2. Latency and Peak-to-peak Latency Measures of the Cervical VEMP

To determine if latency could be used as a diagnostic tool for the identification of Ménière's disease, the P1 and P2 peak latencies were analysed. The inter-latency P1P2 measure was included as an additional evaluation method. The three differing polarities were analysed when sound was presented to both the affected and non-affected ears for the ipsilateral cervical VEMP test. The Kruskal-Wallis one-way ANOVA on ranks statistical method was applied to determine if a significant difference between the early and late Ménière groups and control groups L and R was present.

In contrast to the amplitude measures for the cervical VEMP, the latency measures produced no significant results for any of the measures evaluated when the control groups L and R were compared to the Ménière groups, M1 and M2. This finding differed from the contralateral ocular VEMP responses analysed previously. The means and standard deviations (Table 6.1.2) and the results of statistical analyses (Table 6.1.1), are displayed in Appendix 1.

3.4. Interaural Amplitude Difference Ratio

The interaural amplitude difference ratio (IAD) was applied to both the ocular and cervical VEMP tests to determine its ability to diagnose Ménière's disease. This ratio was applied to all three waveforms analysed in this study, specifically the alternating, rarefaction and condensation waves. The differences between each of these waveforms was investigated to establish whether or not one polarity provided more significant results when applied to the IAD ratio. Four peak-to-peak amplitude measures (N1P1, P1N2, P2N3 and N3P3) were analysed for the ocular VEMP test. Furthermore, the P1N1 and N1P2 peak-to-peak amplitude measures for the cervical response were analysed. The t-test was applied to determine any significant differences between the control group and the Ménière group. When normality or equal variance failed the Mann-Whitney Rank Sum Test was performed.

3.4.1. Contralateral Ocular VEMP IAD Ratio

The IAD ratio for the contralateral ocular VEMP was calculated for the N1P1, P1N2, P2N3 and N3P3 peak-to-peak amplitude measures. Statistical analysis with the t-test failed to determine any significant findings between the control group and Ménière group (Table 6.2.4 in Appendix 1).

3.4.2. Ipsilateral Cervical VEMP IAD Ratio

Results from the standard t-test failed to determine any statistically significant differences between the control group and the Ménière group for the ipsilateral cervical VEMP data. The Mann-Whitney Rank Sum Test revealed a significant difference between the two groups for the N1P2 peak-to-peak amplitude measure with the alternating stimulus as shown in Figure 3.21. The statistical findings and raw data for the IAD ratios of the cervical VEMP are shown in Table 6.1.4 and Table 6.1.5 in Appendix 1.

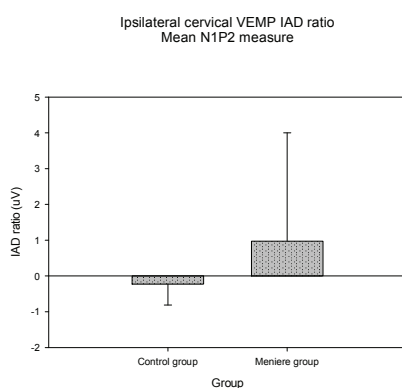


Figure 3.21. Shows the difference in IAD ratio of the N1P2 amplitude measure for the ipsilateral cervical VEMP for the control and Ménière groups.

3.5. Questionnaire

The questionnaire was distributed to all participants in this study to determine if the ocular VEMP test was statistically easier to perform than the cervical VEMP test. The questionnaire also required participants to rank the perceived difficulty of each task from a score between 0 and 100 (with 0 representing easiness of the task). The response rate for the control and patient groups was 86.4% (19 out of 22 of participants) and 66.7% (12 out of 18 participants) respectively.

Results from the questionnaire clearly show that the majority (67%) of participants preferred the ocular VEMP test to the cervical VEMP test (27%). Six percent did not feel there was any difference in difficulty between the two tasks. Participants rated the cervical VEMP test a difficulty of 72 ± 22 compared to the ocular VEMP which had an average score of 54 ± 24 . The paired t-test determined a significant reduction in difficulty of the ocular

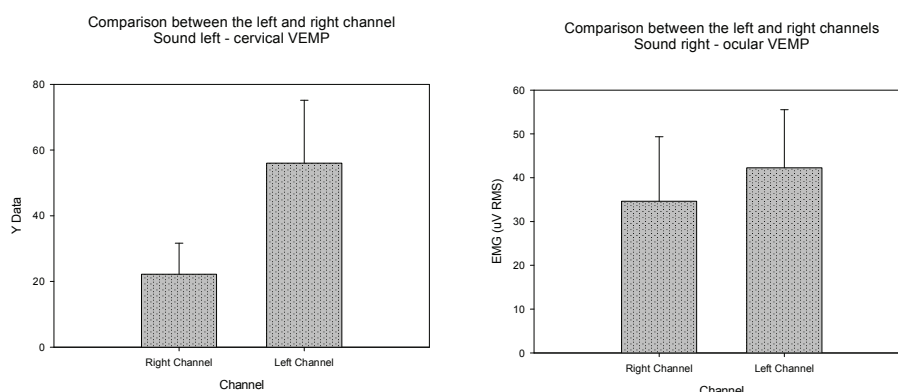
VEMP compared to the cervical VEMP scores ($p = 0.001$). In addition, 76 % of participants felt that the ocular VEMP test could be applied to the general population.

These results suggest that the ocular VEMP test was more tolerable to the cervical VEMP test in this current study.

3.6. EMG

Analysis of the EMG levels of the ipsilateral cervical VEMP data and the contralateral ocular VEMP data was undertaken. The left channel corresponds to presentation of the stimulus to left ear and the right channel corresponds to the presentation to the right ear.

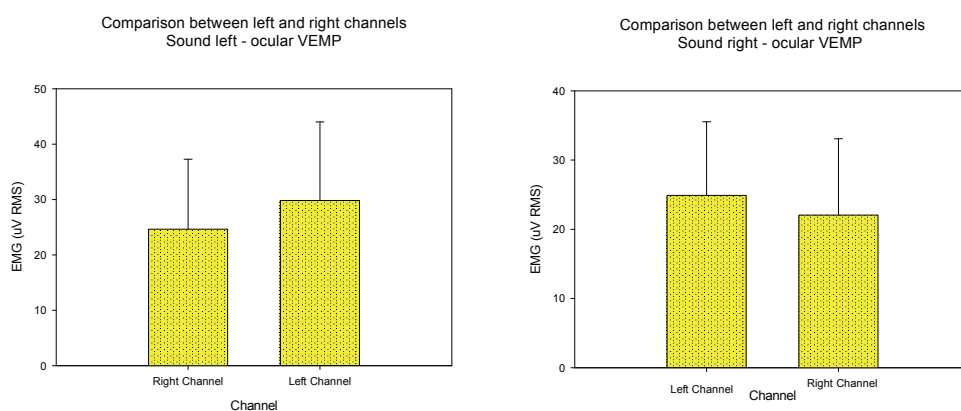
Statistical analyses revealed no significant differences in EMG level between the control group (L + R) and Ménière group (M1 + M2) for the left and right channels of the ocular and cervical VEMP (Table 6.3.4 in Appendix 1).



Figures 3.22 and 3.23. Show the EMG difference between the left and right channels when sound was presented to the left ear for the ipsilateral cervical VEMP for all participants.

Results from the paired t-test comparing the difference between the left and right channels when sound was presented to the left ear for the contralateral ocular VEMP data revealed a significant difference in EMG level ($p = <0.001$). The average EMG level for the left channel was 56.0 μV and for the right ear was 22.2 μV as seen in Figure 3.22. Results when sound was presented to the right ear revealed a significant reduction in EMG level on the right channel ($p = 0.020$). The mean EMG level for the right channel was 34.6 μV , compared to the left channel which had an average EMG level of 42.3 μV , shown in Figure 3.23. This result

indicates an increase in EMG level of the SCM to the side that the sound is presented to for the ipsilateral cervical VEMP when sound was presented to the left ear only.



Figures 3.24 and 3.25. Show the average EMG levels of the left and right channels when sound was presented to the left and right ears for the contralateral ocular VEMP data.

Paired t-test results revealed a significant reduction ($p = <0.001$) in EMG level of the right channel when sound was presented to the left ear. The mean levels for the right and left channels was, 24.9 μV and 29.8 μV , respectively as depicted in Figure 3.24. Sound presented to the right ear however, revealed a reduction ($p = 0.009$) in EMG level in the right channel. The average EMG level was 24.9 μV for the left channel and 22.1 μV for the right as seen in Figure 3.25. These results suggest that the higher level of EMG is likely to occur on the side at which sound is presented to when sound is presented to the left ear only.

CHAPTER FOUR

DISCUSSION

4. Discussion

To examine the relationship between Ménière's disease and VEMPs the established cervical VEMP test was compared to the relatively new ocular VEMP test in participants with no known vestibular pathologies and those with Ménière's disease. This study investigated the VEMP in Ménière's disease further by evaluating the effect of stimulus polarity; the side of presentation of the stimulus (i.e. either contralateral or ipsilateral); and comparisons with the Gibson score and AAONHS criteria. This study was different from several previous ones in that only patients with 'clinically certain' Ménière's disease were included.

It has been previously documented in the literature that ipsilateral presentation of the cervical VEMP and contralateral presentation of the ocular VEMP produce the clearest waveforms than the contralateral and ipsilateral counterparts respectively (Colebatch et al., 1994; Todd et al., 2007). This chapter will discuss the findings from this study in the context of the current literature. This includes discussing the threshold, amplitude, latency and IAD ratio measures used in this study. Conclusions regarding the ability of these measures to diagnose Ménière's disease are also made. In addition, the limitations and future directions of research in this area are discussed.

4.1. Latency

4.1.1. Contralateral Ocular VEMP Latency Review

Results from the contralateral ocular VEMP indicated a significant difference in peak latencies between the control and Ménière's groups for the alternating stimulus. Results from participants with Ménière's disease in the later stages compared to control group R were particularly significant for the P2 latency measure when sound was presented to the affected ear. Dunn's method for post-hoc multiple comparisons determined a statistically significant increase in mean latency for the later stage Ménière's group (30.8 ± 2.2 ms) compared to the control R group (26.8 ± 4.9 ms). No difference between control and Ménière's groups was found with the one-way ANOVA on ranks method when sound was presented to the affected ear (Table 6.2.1, Appendix 1).

One-way ANOVA on ranks performed on the N3 latency measure for the contralateral ocular VEMP showed a statistically significant difference between groups, when sound was

presented to the affected ear and non-affected ears, and the control groups (Table 6.2.1, Appendix 1). However, further analysis applying Dunn's method for post-hoc multiple comparisons did not determine a difference between any of the patient groups.

4.1.2. Ipsilateral Cervical VEMP Latency Review

In contrast, the one-way ANOVA on ranks test applied to the ipsilateral cervical VEMP results did not differentiate between either the control or Ménière's groups for the P1, N1 and P2 peak latencies. Similarly the P1P2 peak-to-peak latency measure failed to distinguish between the control and patient groups. These measures failed to determine any differences when sound was presented to either the affected or non-affected ears for the alternating stimulus (Table 6.1.1, Appendix 1).

4.1.3. Summary of Cervical and Ocular VEMP Latency Measures

Overall, the contralateral ocular VEMP produced the only statistically significant result when differentiating between the control and Ménière's groups for a latency measure (P2). Unfortunately, the P2 peak latency result did not reach statistical significance between the control and early Ménière's group. Therefore, the P2 latency measure can only be applied to differentiate between control participants and participants with stage 3 or 4 Ménière's disease. The P2 latency measure does provide evidence that the ocular VEMP is more sensitive in determining a latency difference between control and Ménière's participants compared to the cervical VEMP. In addition, this result provides evidence for prolongation of P2 latency in participants with Ménière's disease in the later stages.

Current literature has explored the ability of peak latency measures to distinguish between control and Ménière's groups with the cervical VEMP. Results from the Osei-Lah et al. (2008) study determined no significant difference in P1 or N1 peak latency in ears with acute endolymphatic hydrops (15.7 ± 0.9 ms and 23.7 ± 0.9 ms) compared to the control group (15.0 ± 2.2 ms and 23.0 ± 2.5 ms) at threshold. As would be expected, their results did not reveal a significant difference between the control and Ménière's groups when sound was presented to the non-affected ear (15.1 ± 0.8 ms). Results from de Waele et al. (1999) also confirmed no significant difference in the P1 and N1 latencies between control and Ménière's participants. In contrast, the Akkuzu et al. (2005) study determined a prolonged P1 latency of

15.0 \pm 1.5 ms for the Ménière's group compared to the control group (13.7 \pm 1.0 ms) with the cervical VEMP test. To our knowledge, no current literature compares the latency between control participants and those with Ménière's disease for the ocular VEMP peaks. However, results from this study indicate a difference between control and Ménière's groups when measuring latency.

It is expected that latency is not affected by saccular hydrops as a result of Ménière's disease as changes in latency are thought to arise from changes in the conducting pathways of the sacculo-collic reflex pathway for the cervical VEMP (Rauch et al. 2004b). However, a neural delay at the level of the receptor organ may contribute to changes in response latency. Studies by Young et al. (2003), Murofushi et al. (2001) and Ochi et al. (2001) have confirmed this and determined that cervical VEMP latency measures are stable in Ménière's disease. Evidence from the cervical VEMP data in this study supports this theory. In contrast, the results from the current study for the ocular VEMP data suggest that the sacculo-ocular reflex pathway may not be as stable.

Hydrops is likely to affect the utricle more severely than the saccule owing to the finding by Uzun-Coruhlu et al. (2007) that the utricle is only partially attached to the temporal bone. It is interesting then to note that the second most common site of endolymphatic hydrops is the saccule possibly due to its close proximity to the endolymphatic duct. The mechanisms for this build up of endolymph is relatively unknown, however it is hypothesised that osmotic, hydrostatic and changes in permeability of ion channels are responsible for the Ménière's symptoms. These abnormalities could cause an abnormal flow of ions across the labyrinthine membrane stimulating vestibular sensory cells. In addition, it is likely that distension as a result of hydrops causes deficits in mechanoelectrical transduction (Paparella & Djalilian, 2002), as the outer hair cell stereocilia are deflected into a less sensitive position (Salt, 2004). While it is not certain how hydrops would mechanically affect the saccular macula (which is anchored to bone) it is possible that the organ could be affected by one or more of the other pathological mechanisms. Overall, it is relatively clear that the abnormal VEMP responses suggest an alteration in the normal physiology of either the inferior vestibular nerve or the saccule in patients with Ménière's disease (Akkuzu et al., 2006).

Studies by Basta et al. (2005) and Su et al. (2004) investigated the effect of ageing on the cervical VEMP response and found no significant change in latency with age. In contrast, Lee

et al. (2008) found a prolongation of the first two peaks of the cervical VEMP with age. The effect of age on the ocular VEMP was briefly discussed by Iwasaki, Smulders, Burgess, McGarvia, Macdougall, Halmagyi, and Curthoys (2008) whom found a statistically significant increase in N1 latency with age. In this study, control participants were not age-matched to Ménière's participants, and as a result, there was a statistically significance difference in the ages of the two groups ($p \leq 0.001$). As a consequence, the affect of age may have caused the present study to underestimate or overestimate the ability of the VEMPs to diagnose Ménière's disease. This limits the ability of results from this study to be generalised to the population as a whole. Further investigations into the effect of age and the ocular VEMP are needed to provide evidence to exclude its effects when diagnosing Ménière's disease.

In conclusion, the P2 latency measure for the contralateral ocular VEMP when sound is presented to the affected ear suggests a difference between control group R participants and participants with late-stage Ménière's. Distribution plots of the control and Ménière's results would provide further evidence for this difference.

4.2. Amplitude

4.2.1. Contralateral Ocular VEMP Amplitude Review

When alternating stimuli were used to evoke the contralateral ocular VEMP, statistically significant differences were found in the amplitudes of the peaks N1, P1 and N2 between the Ménière's and control groups (Table 6.2.1, Appendix 1). Dunn's method for post-hoc multiple comparisons showed a significant reduction in amplitude between control group L ($1.9 \pm 0.7 \mu\text{V}$) and the early Ménière's group ($0.6 \pm 1.0 \mu\text{V}$) for N1 when sound was presented to the affected ear. As might be expected, the same analysis performed on the non-affected ear failed to determine a statistically significant difference between the groups.

P1 amplitude results indicated a significant reduction in amplitude of the late Ménière's group compared to control group R when sound was presented to both the affected and non-affected ears. For the affected ear data, the mean amplitude for the late Ménière's group was $0.8 \pm 1.0 \mu\text{V}$ compared to control group R which was $2.7 \pm 1.1 \mu\text{V}$. A similar reduction in amplitude ($0.1 \pm 1.2 \mu\text{V}$) was determined between control group R and the late Ménière's

group when sound was presented to the non-affected ear. Dunn's method for post-hoc multiple comparisons revealed a statistically significant reduction in amplitude of the early Ménière's group compared to control group L for the N2 amplitude measure. The mean amplitude for control group L and the early Ménière's group was $-2.7 \pm 1.9 \mu\text{V}$ and $0.4 \pm 1.0 \mu\text{V}$ respectively. Results using Dunn's method failed to determine any statistically significant findings when sound was presented to the non-affected Ménière's ears. Analysis of the N3 amplitude data with sound presented to the affected ear revealed a significant decrease in amplitude of the peak in early and late Ménière's groups compared to control group L. N3 amplitude data from the non-affected ear was not significantly different between the groups.

4.2.2. Ipsilateral Cervical VEMP Amplitude Review

Results from the cervical VEMP indicated a reduction in peak amplitude for the early and late Ménière's groups compared to the control groups L and R (Table 6.1.1, Appendix 1). Analysis applying Dunn's method for multiple comparisons for P1 showed that the P1 amplitude for both the early and late Ménière's groups was significantly smaller than that of control group L when sound was presented to the affected ear. The mean amplitudes for control group L, early Ménière's and late Ménière's groups was $54.9 \pm 45.9 \mu\text{V}$, $14.1 \pm 4.2 \mu\text{V}$ and $9.0 \pm 4.5 \mu\text{V}$ respectively. Sound presented to the non-affected ear for P1 also reached significance between both control groups L and R and the late Ménière's group.

Dunn's method for post-hoc multiple comparisons showed significant reductions in P1N1 amplitude between both L and R control groups and the early and late Ménière's groups when sound was presented to the affected ear. The mean amplitude of control group L and R were $108.9 \pm 99.0 \mu\text{V}$, $107.4 \pm 83.1 \mu\text{V}$, respectively, and the mean amplitudes for the early and late Ménière's groups were, $24.3 \pm 8.8 \mu\text{V}$ and $26.3 \pm 10.4 \mu\text{V}$, respectively. Compared to the P1, N1, N1P2 amplitude measures the P1N1 measure reached statistical significance between both Ménière's groups with either control group L or R. Presentation of the alternating stimulus resulted in a statistically significant difference between both control groups and the late Ménière's group ($41.0 \pm 32.8 \mu\text{V}$) for the cervical VEMP.

4.2.3. Summary of Ocular and Cervical VEMP Amplitude Measures

In summary, both the cervical and ocular VEMP tests showed a statistically significant reduction in amplitude for the affected and non-affected ear Ménière's patient data compared to the control groups. The P1N1 amplitude measure showed the largest differences between the control and Ménière's groups for the cervical VEMP when sound was presented to the affected ear which suggests that it might be potentially strong measure of Ménière's disease. The N3 amplitude measure provided the most statistically significant results for the ocular VEMP as seen in Table 6.2.1 in Appendix 1. In particular, it indicated a difference between both the early and late stages of Ménière's disease. The data from the affected ear data produced more statistically significant results, in terms of a Ménière's diagnosis, compared to the non-affected ear data in all cases discussed.

Reduction in amplitude of the cervical VEMP response has been repeatedly shown in patients with endolymphatic hydrops (Rauch et al., 2004a; Rauch et al., 2004b; Ohki et al., 2002; Akkuzu et al., 2006; Murofushi et al., 2001). In addition, Chihara et al. (2007) applied the ocular VEMP to three participants with Ménière's disease, two of which revealed a decreased amplitude of the oVEMP and an absent oVEMP response in the affected ear. In contrast, the cervical VEMP test revealed one abnormal VEMP response from one participant out of the three when sound was presented to the affected ear. The abnormal cervical VEMP findings are thought to be a result of damage to the saccule or inferior vestibular nerve as a result Ménière's disease (Akkuzu et al., 2005). Evidence from the Chihara et al. (2007) also suggests that the abnormal ocular VEMP responses found attributed to saccular hydrops as a result of Ménière's disease. A more comprehensive review on the effects of saccular hydrops is discussed in Section 4.1.3.

Age related decreases in amplitude have been reported in the literature for both the cervical VEMP (Lee et al., 2008; Welgampola & Colebatch, 2001) and ocular VEMP (Iwasaki et al., 2008). These studies suggest that the results found between the Ménière's and control participants in this investigation could be partially due to age, as there was a statistically significant age difference between these groups ($p \leq 0.001$). Future studies should control for this by age-matching the control and patient participants.

A possible limitation of the significant results between the control and Ménière's groups for the amplitude measure of the cervical VEMP is that the level of tonic activation of the SCM is directly correlated to the amplitude of the response (Akin et al., 2004). Similarly, the ocular VEMP response is thought to be a result of EMG activity recorded from the inferior oblique muscle (Todd et al., 2007). Thus, the amplitude of the ocular VEMP is also likely to reflect the amplitude of the response. Any differences between the control and Ménière's groups could be owing to differing levels of activation between these groups. In order to control for this, participants were required to self-monitor activation of the respective muscles via an LED light. In addition, the principal investigator also monitored the EMG level via the UC VEMP programme. All EMG levels were recorded. Analysis of the EMG levels between the Ménière's and control participants revealed no statistically significant differences for the cervical VEMP nor the ocular VEMP (Table 6.3.4, Appendix 1). Therefore, the effect of EMG level is unlikely to contribute to the differences between the patient and control groups discussed. Further investigation of the normalised peak amplitudes would have provided additional evidence for this statement; however this was not performed due to time constraints.

4.3. Threshold

4.3.1. Ipsilateral Cervical VEMP Threshold Review

The threshold of the response was determined as the lowest intensity level at which a repeatable waveform could be visualised by the principal investigator. The threshold of the ipsilateral cervical VEMP responses for the control group for the alternating, condensation (positive) and rarefaction (negative) stimuli were 101.4 ± 8.8 dB SPL, 98.8 ± 10.6 dB SPL and 101.2 ± 9.2 dB SPL, respectively. These values were not significantly different from the thresholds of participants with Ménière's disease, when sound was presented to both the affected and non-affected ears (one-way ANOVA on ranks test). The thresholds for the affected ear were 101.1 ± 5.1 dB SPL, 102.3 ± 7.9 dB SPL and 103.3 ± 4.6 dB SPL, for the alternating, rarefaction (negative) and condensation (positive) stimuli, respectively. The non-affected ear thresholds were 99.9 ± 9.1 dB SPL for the alternating stimuli, 99 ± 8.9 dB SPL for the rarefaction (negative) stimuli, and 100.5 ± 7.9 dB SPL for the condensation (positive) stimuli.

4.3.2. Contralateral Ocular VEMP Threshold Review

The affected ear thresholds for the contralateral ocular VEMP waveforms did not differ significantly among participant groups or with stimulus polarities. In contrast, when sound was presented to the non-affected ear for the condensation (positive) stimuli, a significant reduction in threshold between the control (99.0 ± 5.3 dB SPL) and Ménière's groups (85.1 ± 33.9 dB SPL) was found with the one-way ANOVA on ranks test

4.3.3. Summary of Ocular and Cervical VEMP Thresholds

The threshold at which either of the VEMP waveforms could first be detected was not able to be used to differentiate between the Ménière's and control groups when sound was presented to the affected ear. This was true for the alternating, condensation (positive) and rarefaction (negative) stimuli. Non-affected ear data using the one-way ANOVA method revealed a significant difference between the groups for the ocular VEMP, with the condensation (positive) stimulus only. Further analysis with Dunn's method for post-hoc multiple comparisons found no statistically significant differences. This provides some evidence that the ocular VEMP test is more sensitive in detecting Ménière's disease in the non-affected ear with the threshold measure compared to the cervical VEMP. However, we cannot exclude the possibility that this difference was due to the age differences between the groups.

The lack of statistically significant findings for the threshold measure suggests that it is a poor method of differentiating between the control and Ménière's groups. These threshold findings are in contrast to studies by Rauch et al. (2004b) and Lin et al. (2006) who described elevations of cervical VEMP threshold of their Ménière's group compared to controls. In agreement with our findings, Osei-Lah et al. (2008) found no significant differences between the VEMP thresholds of their control and Ménière's groups. The current study cannot be directly compared with this one, however, as 10% of the participants in their patient group had possible or probable Ménière's, as opposed to 'clinically-confirmed' Ménière's. Chihara et al. (2007) investigated the threshold of the cervical and ocular VEMPs, however a comparison of thresholds was not made between control and Ménière's ears.

The effect of EMG level in the determination of each subject's threshold is unlikely to explain to the lack of significant findings in this case. This is owing to the fact that interleaved

stimuli were applied during the testing phase. Interleaved stimuli has the advantage of presenting four different intensities in quick succession and consequently, at essentially the same EMG level. However, this does not exclude the fact that the EMG level may have been different between recordings and subjects. In light of this, the threshold measure was still not a sensitive measure to diagnose Ménière's disease in this study.

The lack of significant findings is more likely owed to the small patient group. Furthermore, participant fatigue is likely to be a factor. Participants whom struggled to maintain neck contraction and the superomedial gaze throughout cervical and ocular VEMP testing potentially has a lower threshold than established in this study. The difficulties determining a response by the lead investigator could also account for some of the discrepancies between this study and published studies.

In conclusion, the ocular and cervical VEMP threshold test was a poor method of differentiating between participants with Ménière's disease and healthy participants. The establishment of thresholds was difficult because they had to maintain active contraction, and subjective as only one investigator was analysing the waveforms. More than one investigator at the time of testing would have reduced the subjectivity when establishing threshold.

4.4. IAD ratio

IAD ratio results revealed no statistically significant findings with the t-test for the N1P1, P1N2, P2N3 and N3P3 peak-to-peak amplitude measures for the ocular VEMP. This was consistent for all polarities investigated. Statistical analysis with the Mann-Whitney Rank Sum Test for the cervical VEMP produced a single significant result ($p \leq 0.015$), between the control and Ménière's groups, for the N1P2 peak-to-peak amplitude measure with the alternating stimulus.

The IAD ratio was included as part of the analysis of Ménière's disease because the amplitude of the response in the affected ear tends to be reduced as a result of the disease (Rauch et al., 2004b). Young et al. (2003) provided evidence of a difference in IAD ratios between each stage of Ménière's disease (total $n = 40$). Their results suggested that size of the IAD ratio was related to the progression of the disease. In addition, the Young et al. (2002)

study found a significant difference in IAD ratio between the participants with an augmented VEMP and the control group.

Investigations of asymmetry, similar to the IAD ratio, between the affected and non-affected ear exist. Rauch et al. (2004) investigated the asymmetry between the affected and non-affected ears in patients with Ménière's disease but failed to determine any statistically significant findings. There was however, an overall trend for greater asymmetry within the Ménière's group compared to controls. Iwasaki et al. (2008) also calculated the asymmetry ratio for the air conduction tone burst ocular VEMP. Results revealed an average asymmetry ratio of $11.7 \% \pm 8.3$ for participants with no known vestibular pathologies. In addition, all participants in this group had a ratio less than 40%.

Overall, the IAD ratio measure did not show any statistically significant findings between the control and Ménière's groups investigated in this study. This result was unexpected owing to the large proportion of statistically significant amplitude measures determined for both VEMP test. Consequently, the IAD ratio could not be applied as a tool to stage Ménière's disease in this study.

4.5. Polarity

The polarity of the stimulus notably rarefaction and condensation stimulus polarities and the averaged waveform were individually analysed. Stimulus polarity has been shown to have significant effects on the amplitude and latency of auditory evoked potentials, such as the ABR (see Hall, 2007, for a review). The aim of this study was to determine if a particular polarity provided more statistically significant results for a particular measure. Latency results from the ocular VEMP data produced similar results for the condensation (positive) and alternating stimuli. The rarefaction (negative) waveform produced twofold more statistically significant results than the previous two stimuli (Table 6.2.1, Appendix 1) making it the preferable polarity for investigating latency differences.

Overall results for the cervical VEMP amplitude measures (including affected and non-affected ear data) indicate that the alternating and condensation (positive) polarities produce a greater number of statistically significant results compared to the rarefaction (negative) stimulus. The condensation and alternating polarities revealed statistically significant results

for 70% and 80% of amplitude measures investigated. The rarefaction polarity only determined statistically significant results for 40% of amplitude measures for the cervical VEMP. In contrast, stimulus polarity had no effect on the percentage number of statistically significant results for the ocular VEMP. The three polarities, rarefaction, alternating and condensation stimuli all produced significant results for 65% of the amplitude measures analysed.

In the determination of a significant difference between the control and Ménière's groups for the threshold measure the condensation (positive) stimulus was superior to the other polarities investigated. More specifically, the condensation was the only polarity which determined a statistically significant finding for the threshold measure of the ocular VEMP. IAD ratio results revealed one statistically significant result including both VEMP tests. This result was from data of the alternating stimulus for the cervical VEMP test.

To our knowledge no current literature discusses the effect of stimulus polarity on the ocular nor cervical VEMP responses. In addition, few studies mention the polarity of the stimulus used. The most frequent polarity, from the literature reviewed in this study, for eliciting a cervical VEMP was the alternating stimulus (Rauch et al., 2004a; Rauch et al., 2004b; Lin et al., 2006; Rosengren et al., 2005; Todd, 2003 and Todd et al., 2007). In addition, the rarefaction stimulus was also applied in a number of cases (Magliulo et al., 2004; Akin et al., 2004; Ochi & Ohashi, 2003; Sheykholsami & Kaga, 2002; Heide et al., 1999). One study by Timmer et al. (2006) recorded both sets of data for the rarefaction and condensation stimuli. The results for each polarity were not individually analysed, however. Instead they were averaged to form data which represented an alternating stimulus. Two studies investigating the ocular VEMP used an initial rarefaction stimulus (Wang et al., 2009; Chihara et al., 2007) whilst the Todd et al. (2007) used an alternating stimulus.

Owing to the lack of specification of polarity used in current literature, as well as the absence of condensation stimuli, the investigation of stimulus polarity is clearly warranted. Results from the current study suggest that the application of differing stimulus polarities for VEMP measures can play a role in differentiating between patients with and without Ménière's disease. Further investigations of the effects of stimulus polarity are needed for clinical applications.

4.6. Staging

The ability to determine the effect of stage on the measures we investigated in this study was hampered by the small sample size in the patient group. As a consequence, this study could only evaluate the participants with Ménière's disease in broad categories – specifically, the early Ménière's group (data from participants in stages 1 and 2) and late Ménière's group (data from participants in stages 3 and 4).

The N3 and P1N1 amplitude measures of the ocular and cervical VEMPs, respectively, were the only results which showed statistically significant differences between both the Ménière's and control groups. In particular, a significant reduction in P1N1 amplitude was reached between both L and R control groups and the early and late Ménière's groups when sound was presented to the affected ear. Results from the N3 amplitude data with sound presented to the affected ear revealed a significant decrease in amplitude of the early and late Ménière's groups compared to control group L. Unfortunately, neither measure was able to differentiate between the early and late Ménière's groups.

This study is not the only study which had to re-group the Ménière's results. Akkuzu et al. (2006) had to compare the percentage of abnormalities between their stage I patient data (35.7%) to their combined stage II, III and IV data (83.3%) due to a small patient group. As a result they could not compare the abnormalities between stage for the cVEMP, and the broad comparison made still failed to determine a statistically significant difference.

Overall, the N3 and P1N1 amplitude measures of the ocular and cervical VEMP results were the only measures which showed a significant difference between the control and both Ménière's groups, early and late. The inability of these measures to distinguish between the early and late Ménière's groups suggests that they cannot be used as a way of staging Ménière's disease, even in broad categories. Studies which investigate the ability of the ocular and cervical VEMPs to stage the disease in the future may find statistically a significant result if a larger patient group is implemented.

4.7. Conclusion

Selective stimulation of the saccule by intense air conduction stimuli has been repeatedly investigated in the literature. The pathway from the saccule to the active sternocleidomastoid (SCM) muscle is thought to encompass a three neuron arc, with a resultant biphasic waveform being measureable over the active SCM muscle after filtering and averaging. This waveform is termed the cervical vestibular evoked myogenic potential and has been shown to represent the integrity of the saccule. A similar VEMP waveform can be recorded over the inferior oblique muscle. This waveform consists of three negative and positive peaks. The pathway from the saccule to the inferior oblique muscle is thought to represent a disynaptic pathway.

Studies applying the VEMP tests to participants with no known vestibular pathologies, but with profound hearing loss, determined that these tests must be a result of vestibular and not cochlear function. The current study also investigated the VEMP responses in a participant (p18) with a bilateral profound hearing loss. Both ocular and cervical VEMP responses could be obtained in this participant, confirming previous reports.

Instructions given to participants played a significant role in the acquisition of the ocular and cervical VEMP responses. During the trial period of the cervical VEMP the principal investigator noted that participants produced a larger response when instructed to turn their head hard to the contralateral side of stimulation before rising. Participants confirmed that this made the task easier and their head raised less during testing as a result. Acquisition of the ocular VEMP could also be improved if the participant was instructed to look directly at the ceiling before shifting their gaze into the superomedial position.

Owing to current evidence in the literature that the VEMP responses reflect the integrity of the saccule, this study employed the VEMP in the investigation of Ménière's disease. The pathogenesis of this disease is unclear, however literature suggests that endolymphatic hydrops of the saccule results as a consequence. It is therefore logical to expect that application of the VEMP test is likely to be altered in patients with Ménière's disease due to the distension of the saccule.

This study recorded both the ocular and cervical VEMP responses in eighteen participants with 'clinically certain Ménière's disease' and compared the responses to twenty-two

participants with no known vestibular disorders. The term ‘clinically certain’ Ménière’s disease, was developed by otolaryngologist Prof Jeremy Hornibrook (MBCChB, FRACS). Criteria included the use of EcochG to determine endolymphatic hydrops in conjunction with the Gibson score and AAOHNS criteria to ensure that all participants included in this study had Ménière’s disease. The criteria applied in this study is understood by Prof Jeremy Hornibrook to be the closest diagnosis to the ‘definite’ diagnosis of Ménière’s disease, which can only be given after endolymphatic hydrops is established at autopsy. The study by Ribeiro et al. (2005) was the only study reviewed in this study which included EcochG in the determination of Ménière’s disease for their patient group. The majority of studies reviewed applied the AAOHNS criteria for their Ménière’s patient groups. In contrast, two studies reviewed included participants with probable or possible Ménière’s disease (Cheng & Young, 2006; Osei-Lah et al. 2008). These studies cannot conclude, therefore, that their results are directly attributed to Ménière’s disease, unlike the current study.

The strict criteria used in this study limited the number of participants in the patient group. The lack of significant findings for the threshold and IAD ratio measures may be attributable to this. In addition, the findings from this study cannot be generalised owing to the small size and age range of the patient and control groups. In spite of this, the study does provide evidence that the ocular VEMP test can be applied as a new method for diagnosing Ménière’s disease.

The principal aim of this study was to compare the ability of the ocular VEMP to diagnose Ménière’s disease compared to the well-established cervical VEMP. The statistical results between the two tests were relatively similar for the amplitude measures. Furthermore, the amplitude measures produced more statistically significant results compared to the threshold, IAD and latency measures in this study. The ocular VEMP produced significant results for the threshold and latency measures, whilst the cervical VEMP produced results for the IAD measure. To further distinguish between the two tests a questionnaire was developed. The questionnaire was given to each participant to establish if the ocular VEMP was easier to perform than the cervical VEMP. The motive for this investigation was due to the muscular strain that is required to perform the cervical VEMP, which can immediately exclude VEMP testing in neonates and elderly (Chihara et al., 2007; Iwasaki et al., 2007). Results from the questionnaire revealed that 67% of the 34 participants that responded preferred the ocular VEMP compared to the cervical VEMP. In addition, participants rated the cervical VEMP test

a difficulty score of 72 ± 22 compared to the difficulty of the ocular VEMP score of 54 ± 24 . A statistically significant difference between these scores ($p = 0.001$) was reached. Overall, the results from the questionnaire suggest that the ocular VEMP was significantly easier to perform than the cervical VEMP.

A number of statistically significant differences between the control and patient groups for the non-affected ear data, for the amplitude measures in particular, suggest that both the ocular and cervical VEMP tests may have the ability to detect asymptomatic hydrops. However, we cannot exclude the possibility these results were due to age related differences between the groups. In addition, ECochG was not routinely performed in the asymptomatic ear of participants in the patient group, thus reducing the likelihood of a true difference. In light of this, the Lin et al. (2006) study determined an elevation in threshold in the non-affected ear of 27% in their patient group. These results suggest that further investigation into the ability of VEMPs to detect asymptomatic hydrops in patients with unilateral Ménière's disease is warranted.

The evidence from the current study indicates that the ocular VEMP is as useful a tool in diagnosing Ménière's disease as the cervical VEMP. In addition, before clinical application of the ocular VEMP can proceed, large studies determining the amplitude, latency, IAD ratio and threshold age-matched norms need to be published. For example, the Basta et al. (2005) study is one study that has attempted to determine the norms for the cervical VEMP test. In addition, the ocular VEMP data from this study could be used as an initial estimate for determining differences between control and Ménière's participants.

4.8. Limitations

4.8.1. Participants

A small proportion of results failed to determine statistically significant results between the control and Ménière's groups. This can largely be attributed to the small sample size of the experimental group. In particular, there was a small amount of participants in each stage of Ménière's at the time of testing, with two participants in the second and fourth stages, for example. The study also suffered from the fact that the majority of the participants in the experimental group were in the latest stages of the disease. Furthermore, a proportion of the

participants in the experimental group, p7, p8 and p14, had not experienced vertigo attacks for a significant period of time and were likely to be in the ‘burn-out’ stage of the disease.

A limitation of ECoChG in this study was the period between the time of testing of the ECoChG and the VEMP test. In an attempt to control for this, audiometry was applied to determine if participants had a hearing loss at the time of testing, and thus endolymphatic hydrops.

The current study had a lack of age-matched controls and therefore, the effect of age on the ocular and cervical VEMP responses was not controlled for in this study. For this reason, we cannot exclude the possibility that the differences documented between the control and experimental groups are not due to age. Johnsson & Hawkins (1972) described a degeneration of saccular neuroepithelium with age. In addition, the saccular nerve indicated degeneration and a decrease or complete loss of saccular otoconia beginning from the age of 30. Furthermore, the Kerber, Ishiyama, and Baloh (2006) study suggested a significant decline in optokinetic nystagmus, the visual-vestibulo-ocular reflex and the vestibulo-ocular reflex due to age. A similar age-related decline in amplitude and threshold has been established for the vestibulo-collic reflex pathway (Welgampola & Colebatch, 2001).

Physical limitations of a number of participants reduced the amount of information gathered at the time of testing. For example, participants p6, n8 and n10 suffered from a reoccurring stiff neck, that limited their ability to maintain activation of their SCMs, required to elicit the cervical VEMP response. Similarly, participant p11 suffered from a sore back and had difficulty lying in the supine position for the required testing time.

Recruitment produced two limitations in this study. Firstly, participant n13 had received gentamicin therapy in an effort to relieve the symptoms of Ménière’s disease. This approach destroyed the participants’ hair cells in his cochlea and vestibular system (Perez, Martin, & Garcia-Tarpia, 2003) on the right side preventing the investigator from staging this ear, as a profound hearing loss had resulted. Furthermore, without the vestibular hair cells, cervical and ocular VEMP testing could not be performed as the normal transduction pathway utilised by the VEMP was severely compromised. In addition, during the recruitment stage it was clear that a significant portion of patients with Ménière’s disease in the wider Canterbury region had received gentomycin therapy, thus immediately excluding them from this study.

During ocular VEMP testing it was clear that two participants (p9) and (p14) fell into a sleep like state. This reduced the EMG level significantly. In addition, during ocular VEMP testing, one participant (n19) had watering eyes which made them feel uncomfortable. Dizziness was another factor which made one participant (p4) uncomfortable during both the ocular and cervical VEMP tasks.

Analysis of the cervical and ocular VEMP, left and right control ears, revealed statistically significant differences between the ears (see Appendix 1). In particular, the cervical VEMP threshold and P2 latency measures, and a number of amplitude and latency measures for the ocular VEMP, resulted in significant differences between the control ears. This finding was unexpected as none of the participants in this control group, to their knowledge, suffered from any vestibular pathologies or symptoms. Furthermore, the left speaker of the headphone was applied to both the left and right ears, excluding the possibility of a difference between the left and right speakers of the headphone. To compensate for these differences all statistical analyses were performed with both the left and right control ear data.

4.8.2. Technique

Positioning of electrodes for the ocular VEMP under the eye (Todd et al., 2007) was considerably easier than the cervical VEMP. The cervical VEMP approach required electrodes to be placed over the participants SCMs. This was an issue in a few participants whom had SCMs which were difficult to isolate, in particular participant n16. To overcome this, participants were instructed to lie in the testing position before positioning the electrodes.

The impedance between the electrode and the skin was not monitored in this study. Thus it was possible that some electrodes produced significant amounts of extraneous noise during recording. In an effort to reduce this noise wiping the area of interest with alcohol was undertaken.

The rate of 10 Hz for the presentation was faster than previous literature. Many studies adopted the 5 Hz rate of presentation (Wang & Young, 2003; Chihara et al., 2009). During preliminary trials no obvious difference in the latency nor amplitude were found when the cervical and ocular responses at 5 Hz and 10 Hz were compared. Thus, the 10 Hz rate was used to reduce testing time and thus the likelihood of participant fatigue. The monaural

presentation approach was adopted in the acquisition of VEMP responses as the binaural approach is not commonly applied in the literature. It is possible, however, that the binaural approach would have reduced total testing time (Wang et al., 2009) and may have reduced participant fatigue.

The testing time required to determine the threshold of both the ocular and cervical VEMP response was a limitation in the current study. Testing time ranged from 90 minutes up to 210 minutes. The large amount of testing time was due to the number of averaged responses required to remove extraneous muscle noise, equipment noise and background noise from the responses. Furthermore, threshold seeking for both tests meant that anywhere from 6 to 15 runs had to be undertaken for each participant. In an effort to make testing more comfortable, large rest periods between each run were required for a number of participants.

The level of EMG activity was another limitation of the study. Each participant was required to self-monitor their own EMG level by gazing at a LED light. When the light was on, the participant knew that they had achieved the ideal contraction. For some participants the threshold of the LED light had to be reduced due to difficulty maintaining contraction of the SCM and inferior rectus muscle, and from muscular noise produced from heavy breathing and arm and leg movements. The consequence of this was that the amplitude of the response was likely to be reduced. To account for this the EMG level was recorded for each testing scenario. However, no maximum EMG level was enforced resulting in large EMG levels when recording from the extraocular muscles.

The analysis of the later peaks of the ocular VEMP response and the cervical VEMP response also proved to be a weakness of the study. By including these peaks we hoped to define a new marker for diagnosing Ménière's disease however, it proved to make the statistical analysis and consequent results hard to analyse and draw conclusions from.

The analysis of each cVEMP and oVEMP response with the alternating, condensation and rarefaction stimuli had a limitation. The number of sweeps for the rarefaction and condensation waveforms was half of that of the alternating waveforms. Therefore, comparisons between the three stimuli cannot be directly compared.

4.8.3. Equipment

During the preliminary testing phase it was clear that the intensity of the stimulus was limited by the equipment chosen for this study. This limitation resulted in the inability of the equipment to produce stimuli above 114 dB SPL. Therefore, results produced in this study cannot exclude the possibility that different results may have been reached if the stimulus level was greater than 114 dB SPL.

The transducer applied in this study was a pair of circumaural headphones. These headphones were large and relatively heavy. As a result the headphones had a tendency to move during testing, especially during cervical VEMP recording due to the test position required for this response. The investigator had to ensure throughout testing that the headphones moved as minimally as possible to ensure that the intensity reaching the vestibular system was constant between participants.

4.8.4. Peak Picking

Response determination of the VEMPs was undertaken by the principal investigator. This was performed by visualising each response and labelling each peak of interest. The limitation of peak picking was the amount of noise in each response. This was exacerbated by applying a baseline for the measurement of each peak. For a number of responses and participants, in particular n1, p1 and p2, the amount of noise totally overwhelmed the VEMP response. In other responses the amount of extraneous noise distorted the waveform so that few or no identifiable peaks could be observed.

4.9. Further Directions

The current study could only make conclusions regarding early Ménière's, stages one and two, and late Ménière's, stages three and four. Future studies would benefit from having a larger patient group to determine the differences in the cervical and ocular VEMP responses between each stage. Studies with larger sample sizes may provide better evidence for differentiating between each of the stages of Ménière's disease. Other avenues for future research include investigating the effect of polarity of the stimulus in both the cervical and ocular VEMPs in more detail.

5. References

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6. Appendix 1

- Ipsilateral cervical VEMP tables
- Contralateral ocular VEMP tables
- Left and right control ear tables

6.1 Ipsilateral cervical VEMP tables

Measure	Difference between control L and R, M1 AND M2 for the ipsilateral cervical VEMP at 114 dB SPL – sound presented to affected ear				Difference between control L and R, M1 AND M2 for the ipsilateral cervical VEMP at 114 dB SPL – sound presented to non-affected ear			
	<i>n</i>	<i>H</i>	<i>P</i>	<i>DF</i>	<i>n</i>	<i>H</i>	<i>P</i>	<i>DF</i>
<i>Alternating stimulus</i>								
P1 Latency (ms)	49	4.394	0.222	3	52	4.890	0.299	3
P1 Amplitude (μV)	49	18.329	< 0.001**	3	52	12.769	0.005*	3
N1 Latency (ms)	49	6.117	0.106	3	52	1.280	0.734	3
N1 Amplitude (μV)	49	12.558	0.006*	3	52	7.994	0.046*	3
P2 Latency (ms)	49	0.768	0.857	3	51	5.177	0.159	3
P2 Amplitude (μV)	49	1.131	0.770	3	52	3.496	0.321	3
P1N1 Amplitude (μV)	49	17.559	<0.001**	3	52	10.549	0.014*	3
N1P2 Amplitude (μV)	49	10.392	0.016*	3	52	14.902	0.002*	3
P1P2 Latency (ms)	49	2.011	0.570	3	52	6.583	0.086	3
<i>Rarefaction stimulus</i>								
P1 Latency (ms)	51	7.612	0.055	3	51	5.035	0.169	3
P1 Amplitude (μV)	51	7.969	0.047*	3	51	4.993	0.172	3
N1 Latency (ms)	51	6.247	0.100	3	51	1.689	0.639	3
N1 Amplitude (μV)	51	12.196	0.007*	3	51	4.056	0.255	3
P2 Latency (ms)	48	3.231	0.357	3	48	7.441	0.059	3
P2 Amplitude (μV)	48	0.621	0.892	3	48	1.873	0.599	3
P1N1 Amplitude (μV)	51	11.388	0.010*	3	51	4.521	0.210	3
N1P2 Amplitude (μV)	48	6.343	0.096	3	48	10.945	0.012*	3
P1P2 Latency (ms)	48	5.988	0.112	3	48	7.721	0.052	3
<i>Condensation stimulus</i>								
P1 Latency (ms)	43	2.377	0.498	3	47	3.690	0.297	3
P1 Amplitude (μV)	43	18.282	< 0.001**	3	47	11.793	0.008*	3
N1 Latency (ms)	43	0.794	0.851	3	47	5.983	0.112	3
N1 Amplitude (μV)	43	11.312	0.010*	3	47	5.132	0.162	3
P2 Latency (ms)	42	2.080	0.556	3	47	2.130	0.546	3
P2 Amplitude (μV)	42	1.030	0.794	3	46	2.424	0.489	3
P1N1 Amplitude (μV)	43	17.246	< 0.001**	3	46	9.011	0.029*	3
N1P2 Amplitude (μV)	42	8.051	0.045*	3	47	9.840	0.020*	3
P1P2 Latency (ms)	42	1.942	0.585	3	46	4.860	0.182	3

* Significant at 0.05 level ** Significant at 0.001 level

Table 6.1.1 One-way ANOVA on ranks results for ipsilateral presentation with the cervical VEMP test when sound was presented to affected and non-affected MD ears. The amplitude (μV) and latency (ms) values for the P1, P2, and N1 peaks were evaluated in conjunction with the P1N1 and N1P2 inter-amplitude measures and the P1P2 inter-latency measure. All data was compared between the control groups L and R and the two Ménière groups, M1 and M2.

Stimulus	Difference between the control L and R, M1 and M2 groups threshold data for the ipsilateral cervical VEMP – sound presented to non- affected ear				Difference between the control L and R, M1 and M2 groups threshold data for the contralateral ocular VEMP – sound presented to non-affected ear			
	<i>n</i>	<i>H</i>	<i>P</i>	<i>DF</i>	<i>n</i>	<i>H</i>	<i>P</i>	<i>DF</i>
Alternating	57	7.699	0.053	3	54	7.248	0.064	3
Rarefaction	58	3.628	0.305	3	58	2.504	0.475	3
Condensation	58	5.623	0.131	3	58	8.394	0.039	3*

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.1.2 Comparison between each stage including the control, M1 and M2 groups for the contralateral ocular and ipsilateral cervical VEMP thresholds (dB SPL) when sound was presented to the non-affected ear.

	Mean thresholds of the cervical VEMP (dB SPL)					
	Alternating stimulus		Rarefaction stimulus		Condensation stimulus	
	N	Mean	n	Mean	n	Mean
Ménière's disease – sound to affected ear	17	101.059 ± 5.018	17	102.235 ± 7.894	15	103.333 ± 4.577
Ménière's disease – sound to non-affected ear	17	99.882 ± 9.055	17	99 ± 8.839	17	100.471 ± 7.859
Control	40	101.375 ± 8.842	44	98.773 ± 10.508	41	101.195 ± 9.155

Table 6.1.3 Mean and standard deviation (mean ± 1 SD) of the threshold data for the Ménière and control groups for the ipsilateral cervical VEMP. All three stimuli are included.

	Alternating			Rarefaction			Condensation		
	<i>t</i>	<i>p</i>	<i>DF</i>	<i>t</i>	<i>p</i>	<i>DF</i>	<i>t</i>	<i>p</i>	<i>DF</i>
P1N1	-1.112	0.274	32	-1.074	0.290	34	1.237	0.225	32
N1P2	-1.695	0.015*	33	-1.382	0.176	33	-1.382	0.176	33

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.1.4 The t-test results of the P1N1 and N1P2 IAD ratio's for the control and Ménière groups for the ipsilateral cervical VEMP.

		Alternating			Rarefaction			Condensation		
		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
P1N1	Control	22	-0.074	0.523	22	-0.131	0.438	22	-0.109	0.556
	Patient	17	0.321	1.437	17	0.079	0.725	17	-0.365	0.651
N1P2	Control	22	-0.227	0.588	22	-0.803	1.238	22	-0.326	1.020
	Patient	17	0.973	3.026	17	0.310	3.248	17	-4.124	28.118

Table 6.1.5 The mean and standard deviations of the P1N1 and N1P2 IAD ratio's for the control and Ménière groups for the ipsilateral cervical VEMP.

6.2 Contralateral ocular VEMP tables

Measure	Difference between all stages, control, M1 and M2 for the contralateral ocular VEMP at 114 dB SPL – sound presented to affected ear				Difference between all stages, control, M1 and M2 for the contralateral ocular VEMP at 114 dB SPL – sound presented to non-affected ear			
	<i>n</i>	<i>H</i>	<i>p</i>	<i>df</i>	<i>n</i>	<i>H</i>	<i>p</i>	<i>df</i>
<i>Alternating stimulus</i>								
N1 Latency	99	0.608	0.895	3	99	2.303	0.512	3
N1 Amplitude	99	28.535	< 0.001 **	3	99	27.756	< 0.001 **	3
P1 Latency	99	2.468	0.481	3	99	1.403	0.705	3
P1 Amplitude	99	24.368	< 0.001 **	3	99	25.766	< 0.001 **	3
N2 Latency	99	6.759	0.008*	3	99	2.314	0.510	3
N2 Amplitude	99	23.489	< 0.001 **	3	99	21.365	< 0.001 **	3
N1P1 Amplitude	99	7.145	0.067	3	99	10.380	0.016 *	3
P1N2 Amplitude	99	7.505	0.057	3	99	6.141	0.105	3
P2 Latency	99	8.998	0.029 *	3	99	6.598	0.086	3
P2 Amplitude	99	14.985	0.002 *	3	99	14.138	0.003 *	3
N3 Latency	99	10.404	0.015 *	3	99	13.161	0.004 *	3
N3 Amplitude	99	21.205	< 0.001 **	3	99	18.383	< 0.001 **	3
P3 Latency	99	5.381	0.146	3	99	5.894	0.117	3
P3 Amplitude	99	8.808	0.032 *	3	99	8.326	0.040 *	3
P2N3 Amplitude	99	7.644	0.054	3	99	6.607	0.086	3
N3P3 Amplitude	99	1.673	0.643	3	99	2.271	0.518	3
<i>Rarefaction stimulus</i>								
N1 Latency	99	2.140	0.544	3	99	2.271	0.518	3
N1 Amplitude	99	24.574	< 0.001 **	3	99	24.445	< 0.001 *	3
P1 Latency	99	1.562	0.668	3	99	1.132	0.769	3
P1 Amplitude	99	24.432	< 0.001 **	3	99	22.453	< 0.001 **	3
N2 Latency	99	4.755	0.191	3	99	1.491	0.684	3
N2 Amplitude	99	20.730	< 0.001 **	3	99	17.400	< 0.001 **	3
N1P1 Amplitude	99	10.780	0.013 *	3	99	4.748	0.191	3
P1N2 Amplitude	99	2.183	0.535	3	99	3.034	0.386	3
P2 Latency	99	9.023	0.029 *	3	99	11.457	0.009 *	3
P2 Amplitude	99	16.670	< 0.001 **	3	99	14.131	0.003 *	3
N3 Latency	99	8.617	0.035 *	3	99	9.518	0.023 *	3
N3 Amplitude	99	17.124	< 0.001 **	3	99	14.943	0.002 *	3
P3 Latency	99	13.786	0.003 *	3	99	11.956	0.008 *	3
P3 Amplitude	99	7.480	0.058	3	99	5.864	0.118	3
P2N3 Amplitude	99	12.609	0.006 *	3	99	8.628	0.035 *	3

N3P3 Amplitude	99	1.979	0.577	3	99	3.809	0.283	3
<i>Condensation stimulus</i>								
N1 Latency	99	1.911	0.591	3	99	3.955	0.266	3
N1 Amplitude	99	29.974	<0.001 **	3	99	30.022	< 0.001 **	3
P1 Latency	99	1.737	0.629	3	99	3.214	0.360	3
P1 Amplitude	99	20.948	<0.001 **	3	99	23.135	< 0.001 **	3
N2 Latency	99	1.147	0.766	3	99	0.947	0.814	3
N2 Amplitude	99	21.458	<0.001 **	3	99	17.389	< 0.001 **	3
N1P1 Amplitude	99	4.384	0.223	3	99	10.461	0.015 *	3
P1N2 Amplitude	99	3.151	0.369	3	99	4.744	0.192	3
P2 Latency	99	5.427	0.246	3	99	3.522	0.318	3
P2 Amplitude	99	10.638	0.014 *	3	99	8.982	0.030 *	3
N3 Latency	99	4.628	0.201	3	99	8.441	0.038 *	3
N3 Amplitude	99	18.954	<0.001 **	3	99	19.934	< 0.001 **	3
P3 Latency	99	8.933	0.030 *	3	99	8.872	0.031 *	3
P3 Amplitude	99	10.442	0.015 *	3	99	9.893	0.019 *	3
P2N3 Amplitude	99	7.414	0.060	3	99	4.498	0.212	3
N3P3 Amplitude	99	1.771	0.621	3	99	0.709	0.871	3

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.2.1 One-way ANOVA on ranks between all stages for the contralateral ocular VEMP when sound was presented to non-affected and affected ears. The amplitude (μV) and latency measures (ms) N1, P1, N2, P2, N3 and P3 were assessed. The inter-amplitude measures P2N3 and N3P3 were included.

	Mean thresholds of the ocular VEMP (dB SPL)								
	Mean			Negative (rarefaction)			Positive (condensation)		
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
Ménière's disease – sound to affected ear	16	88.500	35.532	16	89.437	35.274	16	89.125	35.206
Ménière's disease – sound to non-affected ear	15	83.467	34.182	14	85.571	37.032	16	85.063	33.930
Control	40	99.500	5.751	40	104.000	6.460	39	99.000	5.324

Table 6.2.2 Mean and standard deviation (mean \pm 1 SD) of the threshold data for the Ménière and control groups of the contralateral ocular VEMP. All three waveform types are included.

Stimulus	Difference between the control L and R, M1 and M2 groups threshold data for the contralateral ocular VEMP – sound presented to affected ear				Difference between the control L and R, M1 and M2 groups threshold data for the contralateral ocular VEMP – sound presented to affected ear			
	<i>n</i>	<i>H</i>	<i>P</i>	<i>DF</i>	<i>N</i>	<i>H</i>	<i>P</i>	<i>DF</i>
Alternating	57	4.376	0.224	3	55	2.681	0.443	3
Rarefaction	58	1.844	0.605	3	56	3.252	0.354	3
Condensation	56	4.631	0.201	3	55	6.828	0.078	3

* Significant at 0.05 level ** Significant at 0.001 level

Table 6.2.3 Comparison between each stage including the control, M1 and M2 groups for the contralateral ocular and ipsilateral cervical VEMP thresholds (dB SPL) when sound was presented to the affected ear using the one-way ANOVA on ranks test.

	Alternating			Negative			Positive		
	<i>t</i>	<i>p</i>	<i>DF</i>	<i>t</i>	<i>p</i>	<i>DF</i>	<i>t</i>	<i>p</i>	<i>DF</i>
NIP1	1.295	0.204	33	0.854	0.399	33	1.295	0.205	30
P1N2	-0.565	0.576	33	0.600	0.553	33	-1.443	0.159	30
P2N3	-0.559	0.581	28	-0.208	0.837	26	0.405	0.688	28
N3P3	-0.180	0.858	26	0.244	0.809	27	0.743	0.464	27

* Significant at 0.05 level ** Significant at 0.001 level

Table 6.2.4 The t-test results of the N1P1, P1N2, P2N3 and N3P3 IAD ratio's for the control and Ménière groups of the contralateral ocular VEMP.

		Alternating			Negative			Positive		
		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
NIP1	Control	22	0.254	0.492	22	0.486	2.632	22	0.246	0.569
	Patient	17	-0.027	0.795	17	-0.15	0.806	17	-0.060	0.764
P1N2	Control	22	0.005	0.791	22	0.136	1.061	22	-4.273	14.104
	Patient	17	0.179	1.027	17	-0.045	0.259	17	33.350	116.426
P2N3	Control	22	0.145	0.688	22	0.124	0.621	22	0.223	0.671
	Patient	17	0.304	0.831	17	0.183	0.874	17	0.099	0.995
N3P3	Control	22	-0.120	2.782	22	4.250	0.980	22	0.371	1.457
	Patient	17	0.053	0.981	17	0.328	1.148	17	-0.028	1.004

Table 6.2.5 The mean and standard deviations of the N1P1, P1N2, P2N3 and N3P3 IAD ratio's for the control and Ménière groups of the contralateral ocular VEMP.

6.3 Comparison between control L and R groups

Measure	Difference between Left and Right Control ears	
	<i>n</i>	<i>p</i>
<i>Alternating waveform</i>		
N1 Latency (ms)	37	0.279
N1 Amplitude (μV)	37	≤ 0.001*
P1 Latency (ms)	37	0.838
P1 Amplitude (μV)	37	≤ 0.001*
N2 Latency (ms)	37	0.133
N2 Amplitude (μV)	37	≤ 0.001*
N1P1 Amplitude (μV)	37	0.535
P1N2 Amplitude (μV)	37	0.043*
P2 Latency (ms)	33	0.366
P2 Amplitude (μV)	33	0.002*
N3 Latency (ms)	32	0.345
N3 Amplitude (μV)	31	≤ 0.001*
P3 Latency (ms)	28	0.007*
P3 Amplitude (μV)	29	0.215
P2N3 Amplitude (μV)	31	0.667
N3P3 Amplitude (μV)	29	0.392
<i>Rarefaction</i>		
N1 Latency (ms)	33	0.239
N1 Amplitude (μV)	33	≤ 0.001*
P1 Latency (ms)	33	0.832
P1 Amplitude (μV)	33	≤ 0.001*
N2 Latency (ms)	33	0.952
N2 Amplitude (μV)	33	≤ 0.001*
N1P1 Amplitude (μV)	33	0.846
P1N2 Amplitude (μV)	33	0.115
P2 Latency (ms)	20	0.709
P2 Amplitude (μV)	20	0.015*
N3 Latency (ms)	18	0.345
N3 Amplitude (μV)	18	0.001*
P3 Latency (ms)	16	0.003*

P3 Amplitude (μV)	16	0.616
P2N3 Amplitude (μV)	16	0.648
N3P3 Amplitude (μV)	16	0.164
<i>Condensation waveform</i>		
N1 Latency (ms)	33	0.151
N1 Amplitude (μV)	33	$\leq 0.001^*$
P1 Latency (ms)	33	0.549
P1 Amplitude (μV)	33	$\leq 0.001^*$
N2 Latency (ms)	33	0.313
N2 Amplitude (μV)	33	$\leq 0.001^*$
N1P1 Amplitude (μV)	33	0.324
P1N2 Amplitude (μV)	33	0.095
P2 Latency (ms)	20	0.219
P2 Amplitude (μV)	20	0.037*
N3 Latency (ms)	22	0.213
N3 Amplitude (μV)	22	$\leq 0.001^*$
P3 Latency (ms)	21	0.027*
P3 Amplitude (μV)	31	0.039*
P2N3 Amplitude (μV)	31	0.664
N3P3 Amplitude (μV)	31	0.880

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.3.1 Standard t-test (left by right) of the contralateral ocular VEMP data at 114 dB SPL for the alternating, condensation and rarefaction stimuli.

Measure	Difference between Left and Right Control ears	
	<i>n</i>	<i>p</i>
<i>Alternating waveform</i>		
P1 Latency (ms)	37	0.771
P1 Amplitude (μV)	37	0.371
N1 Latency (ms)	37	0.756
N1 Amplitude (μV)	37	0.863
P2 Latency (ms)	36	$\leq 0.001^*$
P2 Amplitude (μV)	39	0.481
P1N1 Amplitude (μV)	37	0.632
N1P2 Amplitude (μV)	37	0.448
P1P2 Latency (ms)	37	0.772

<i>Rarefaction waveform</i>		
P1 Latency (ms)	38	0.498
P1 Amplitude (μV)	38	0.395
N1 Latency (ms)	38	0.805
N1 Amplitude (μV)	38	0.947
P2 Latency (ms)	35	0.483
P2 Amplitude (μV)	35	0.526
P1N1 Amplitude (μV)	38	0.685
N1P2 Amplitude (μV)	35	0.361
P1P2 Latency (ms)	35	0.737
<i>Condensation waveform</i>		
P1 Latency (ms)	33	0.392
P1 Amplitude (μV)	33	0.630
N1 Latency (ms)	33	0.596
N1 Amplitude (μV)	33	0.974
P2 Latency (ms)	33	0.610
P2 Amplitude (μV)	33	0.568
P1N1 Amplitude (μV)	36	0.771
N1P2 Amplitude (μV)	33	0.500
P1P2 Latency (ms)	33	0.433

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.3.2 Paired t-test (left by right) for the control group of the ipsilateral cervical VEMP at 114 dB SPL for alternating, rarefaction and condensation stimuli.

Waveform	Difference between left and right control threshold data for the ipsilateral cervical VEMP				Difference between left and right control threshold data for the contralateral ocular VEMP			
	<i>n</i>	<i>t</i>	<i>P</i>	<i>DF</i>	<i>n</i>	<i>t</i>	<i>P</i>	<i>DF</i>
Alternating (dB SPL)	44	-2.938	0.009	17 *	44	0.697	0.494	18
Rarefaction (dB SPL)	44	-1.756	0.096	18	44	0.139	0.891	19
Condensation (dB SPL)	44	-2.787	0.012	18 *	44	1.166	0.259	18

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.3.3 Paired t-test (left by right) results of the control group threshold (dB) data for the alternating, condensation and rarefaction stimuli.

	Sound Left						Sound Right					
	Channel Left			Channel Right			Channel Left			Channel Right		
	<i>n</i>	<i>p</i>	<i>t</i>	<i>n</i>	<i>p</i>	<i>t</i>	<i>n</i>	<i>p</i>	<i>t</i>	<i>n</i>	<i>p</i>	<i>t</i>
Ipsilateral cervical VEMP (μ V)	38	0.482	0.710	38	0.956	-0.055	33	0.209	1.284	33	0.764	0.303
Contralateral ocular VEMP (μ V)	34	0.435	-0.790	34	0.890	-0.140	29	0.383	0.887	29	0.074	1.858

* Significant at 0.05 level

** Significant at 0.001 level

Table 6.3.4. T-test results comparing the EMG levels between the Ménière (M1 + M2) and control (L + R) groups for the ocular and cervical VEMPs.

Appendix 2

- Low risk ethic's approval
- Consent form
- Information form
- Questionnaire

Sarah-Anne McElhinney
Communication Disorders
UNIVERSITY OF CANTERBURY

Dear Sarah-Anne

Thank you for forwarding to the Human Ethics Committee a copy of the low risk application you have recently made for your research proposal “A comparison of Ocular and Cervical Vestibular evoked Myogenic Potentials in the evaluation of different stages of Ménière’s disease”, and for providing clarification on aspects of the project as requested.

I am pleased to advise that this application has been reviewed and I confirm support of the Department’s approval for this project.

With best wishes for your project.

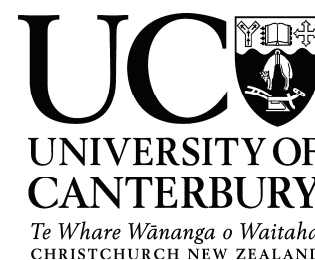
Yours sincerely

Dr Michael Grimshaw
Chair, Human Ethics Committee

College of Science

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Project Information Sheet v2.0, 6th May 2008

Masters of Audiology Thesis Consent Form
 Sarah-Anne McElhinney

A new method of diagnosing and staging Ménière's Disease.

A Comparison of Ocular and Cervical Vestibular Evoked Myogenic Potentials in the Evaluation of Different Stages of Ménière's Disease.

English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Ou te mana'ó ia I ai se faámatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Ioe	Ikai
Cook Island	Ka inangaro au I tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Mandarin	我需要一個翻譯	对	不对
Japanese	通訳の人を希望します。	はい。	いいえ。
Korean	통역이 필요 하세요?	네	아니오

Ethnicity:

- ☐ New Zealand European
- ☐ Māori
- ☐ Samoan
- ☐ Cook Islands Maori
- ☐ Tongan
- ☐ Niuean
- ☐ Chinese
- ☐ Indian
- ☐ Other (such as Dutch, Japanese, Tokelauan). Please state: _____

- 1) I have read and I understand the information sheet (dated 6th May 2008) for volunteers taking part in the study. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- 2) I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
- 3) I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without having to give a reason
- 4) I have had this project explained to me by the principal investigator, Ms Sarah-Anne McElhinney.
- 5) I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports in this study.
- 6) I understand that the results collected in this study will be kept in a secure location for a period of 10 years.
- 7) I understand that this study has received ethical approval from both the Upper South A Regional Ethics Committee and the University of Canterbury's Human Ethics Committee
- 8) I understand that this study requires participant co-operation to maintain eye gaze and neck muscle contraction
- 9) I understand that the results collected in this study will be used to form a Master of Audiology thesis and may be published
- 10) I consent to the use of my data for future related studies, which have been given ethical approval from a Health & Disability Ethics Committee
- 11) I understand that a suitable interpreter will be provided if necessary
- 12) I understand that this study will not directly help the participants but aims to help future patients affected by Ménière's Disease
- 13) I have had time to consider if whether or not to participate in the study
- 14) I would like a copy of the results yes/no
- 15) I agree to my GP or other current provider being informed of my participation in this study yes/no

Participant to sign:

I provide my consent to participate in the study as outlined above. I have read the information sheet and understand the aims and what is required of myself to participate.

Signed Date

Researcher to sign:

I have explained the study to the participant and they are fully aware of the risks of the study. I have witnessed the signing of the consent form above.

Signed Date

College of Science

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Project Information Form v2.0, 6th May 2008



Master of Audiology Thesis:

A new method of diagnosing and staging Ménière's Disease.

A Comparison of Ocular and Cervical Vestibular Evoked Myogenic Potentials in the Evaluation of Different Stages of Ménière's Disease.

Background of the Study

This study is researching a new technique for diagnosing Ménière's Disease, a disease which has debilitating effects for those affected. Ménière's Disease results in attacks of vertigo, tinnitus, aural fullness and fluctuating hearing levels. The exact cause of Ménière's Disease is unknown, but it has been shown to be a pathology of the inner ear. In particular, the cochlea (responsible for hearing) and the saccule (part of the system responsible for balance) are affected. It is now widely accepted that the balance system, including the saccule, can be stimulated by loud sounds presented to the ear. This acoustic stimulation has been shown to result in a measureable electrical response in the neck, called the VEMP (vestibular-evoked myogenic potential). For the response to be measured, however, the muscle of interest must be active – this can be achieved by simply lifting the head up from a laying-down position.

This response can be used clinically to help diagnose a variety of balance disorders. VEMP testing has previously been applied in the analysis of patients with Ménière's Disease, and it has been established that the VEMP response is diminished or absent in patients with Ménière's Disease.

In this study we are exploring a new method of obtaining a response from the vestibular system. In addition to measuring the electrical signal in the neck muscles, we will be measuring a similar signal in the muscles around the eye. The advantage of measuring a signal around the eye is that the participant no longer has to maintain neck activity by holding up their head throughout testing. All that is required when testing for ocular VEMPs is the maintenance of eye gaze straight ahead on a fixed target. We hope that this new method will not only widen the number of people in the population who can now undergo vestibular testing (such as the elderly and young children), but we also hope to find a new and more reliable method of diagnosing Ménière's Disease.

Procedure

The study requires a simple hearing test, which normally consists of pure-tone audiometry and tympanometry, which assesses the condition of the middle ear. This part of the test will be held in the University of Canterbury Communication Disorders Audiology Clinic. Both of these tests are routinely performed on people of all ages, and are not uncomfortable or invasive in any way. The study also requires the testing of the balance system by placing adhesive electrodes on the neck and around the eyes whilst a tone is played into each ear at a loud level (around 95 dB SPL). This level is not harmful or painful. The study requires the neck muscles be contracted by lifting the head from a supine (laying down) position for a period of time, and also requires the maintenance of eye muscle contraction by gazing forward for a period of time. This will be the hardest part of participation for the subject. You will be required to make an appointment and testing will take approximately 1.5 hours and will take place at the University of Canterbury Communication Disorders Electrophysiology Lab.

Will this study help me?

This study will not directly help you but may help people with Ménière's Disease in the future. If we can detect Ménière's earlier, we may be able to treat it earlier.

All the tests are safe and will not cause you any harm. You are free to withdraw from the study as you wish. All results will be sent to you in written and summarised form.

Thank-you for your participation in this study, it is greatly appreciated.

- No material which could personally identify you will be used in any reports on this study.
- All data collected during this study will be held for a period of 10 years.
- The results from this study will go towards a Master of Audiology Thesis.
- With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health & Disability Ethics Committee.
- All testing will be performed at the University of Canterbury Communication Disorders Department, Creyke Rd, Ilam, Christchurch.
- This study has received ethical approval from the Upper South A Regional Ethics Committee and the University of Canterbury's Human Ethics Committee.
- A \$10.00 petrol voucher will be offered as reimbursement for any travel costs incurred as a result of participation in the study.
- If you have any queries or concerns regarding your rights as a participant in this study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.
 - Telephone: (NZ wide): 0800 555 050
 - Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)
 - Email (NZ wide): advocacy@hdc.org.nz
- In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses

and there may be no lump sum compensation payable. If you have ACC cover, generally this will affect your right to sue the investigations. If you have any questions about AC, contact your nearest ACC office or the investigator.

College of Science

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Project Questionnaire v1.0, 12th January 2009

A new method of diagnosing and staging Ménière's Disease.

A Comparison of Ocular and Cervical Vestibular Evoked Myogenic Potentials in the Evaluation of Different Stages of Ménière's Disease.

Name:

Date of birth:

1. During your visit to the department, you were asked to perform two different tasks. Which task was easier to perform? *(Circle one)*

- a. The *ocular vestibular evoked myogenic potential test* where electrodes were positioned under the eye and you were instructed to look upwards.
- b. The *cervical vestibular evoked myogenic potential test* where electrodes were placed on the neck and you were instructed to lift your head up from a supine position (i.e. laying on your back).

The following two questions require you to mark somewhere on a scale from "very difficult" to "very easy". For example, if you thought a task was neither easy nor difficult, you would mark here:



Very
Difficult

Difficult

Neutral

Easy

Very

Easy

2. Indicate on the scale the degree of difficulty you found the cervical vestibular evoked myogenic test where you had to lift your head up from a supine position.



Very
Difficult

Difficult

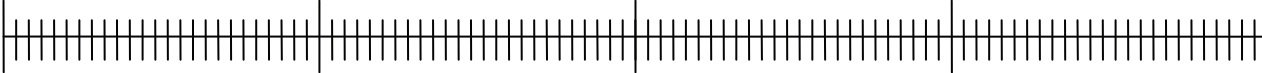
Neutral

Easy

Very

Easy

3. Indicate on the scale the degree of difficulty you found the ocular vestibular evoked myogenic test where you had to maintain your gaze upward.



Very Difficult Difficult Neutral Easy Very Easy

4. Do you have any suggestions that could have made testing more tolerable?

5. If the ocular vestibular evoked myogenic potential test (where electrodes were positioned under the eye and you were instructed to look upwards) proved a reliable method of diagnosing Ménière's disease do you think that this would be an acceptable test for the general population?

6. Do you have any other comments for us?